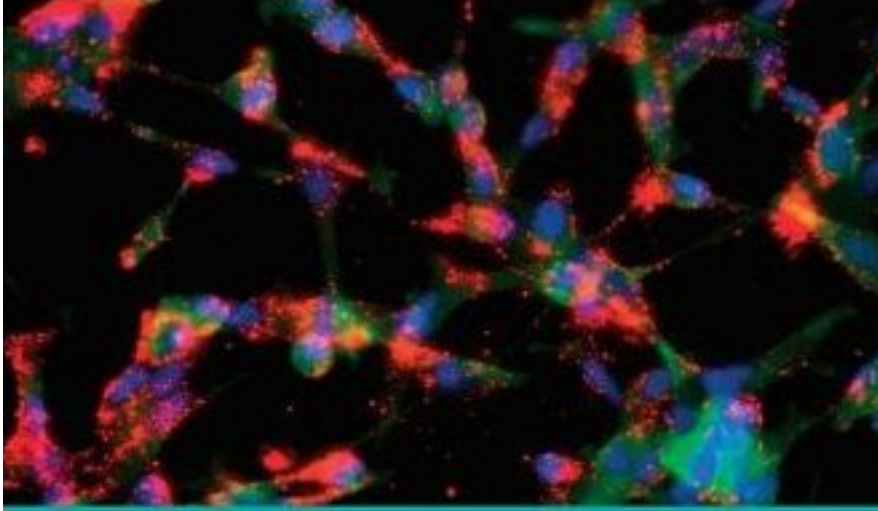

Nanotechnology and Oncology

WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
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Nanotechnology and Oncology

WORKSHOP SUMMARY

Margie Patlak and Christine Micheel, *Rapporteurs*

National Cancer Policy Forum

Board on Health Care Services

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Washington, D.C.
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This study was supported by Contract Nos. HHSN261200900003C and 200-2005-13434 TO #1, between the National Academy of Sciences and the National Cancer Institute and the Centers for Disease Control and Prevention, respectively. This study was also supported by the American Association for Cancer Research, American Cancer Society, the American Society of Clinical Oncology, the Association of American Cancer Institutes, C-Change, the CEO Roundtable on Cancer, Novartis Oncology, and the Oncology Nursing Society. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-16321-7
International Standard Book Number-10: 0-309-16321-8

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM (Institute of Medicine). 2011. *Nanotechnology and oncology: Workshop summary.* Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

Joseph M. DeSimone, University of North Carolina at Chapel Hill
Sanjiv Sam Gambhir, Stanford University
Scott E. McNeil, Nanotechnology Characterization Laboratory and National Cancer Institute
Richard C. Pleus, INTERTOX, Inc.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Melvin Worth.** Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authors and the institution.

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1

Introduction

If you want to summarize the promise of nanomedicine in one word, that word is "control." For 3,000 years we have been giving drugs to patients, and the drugs go wherever they want and can cause toxicity. They may treat the right things, but we lose control. The promise of nanomedicine is to allow you to bring back that control. Imagine the day you can say, "drug, come here; drug, turn on; drug, turn off." That will be the day that we have revolutionized medicine. To be able to engineer that in a small molecule is almost impossible. There are not enough elements in a small molecule to allow you to build in those controls. Whereas in nanomedicine, you theoretically can program that particular nanomaterial to do what you want it to do using local or remote signals. (Li, 2010)

Increasingly, the nature of cancer and how to prevent, diagnose, and treat it is being understood. Biological interactions important for cancer pathophysiology include genetic, intracellular, and intercellular processes—many of which take place on a scale between 1 nanometer and several microns. According to the National Nanotechnology Initiative, "nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers (see Figure 1), where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale" (NNI, 2010). Nanotechnology has the potential to translate recent discoveries in cancer biology into clinical advances in oncology.

Consequently, public investment in nanotechnology for cancer continues to increase, and medical products based on nanotechnology are

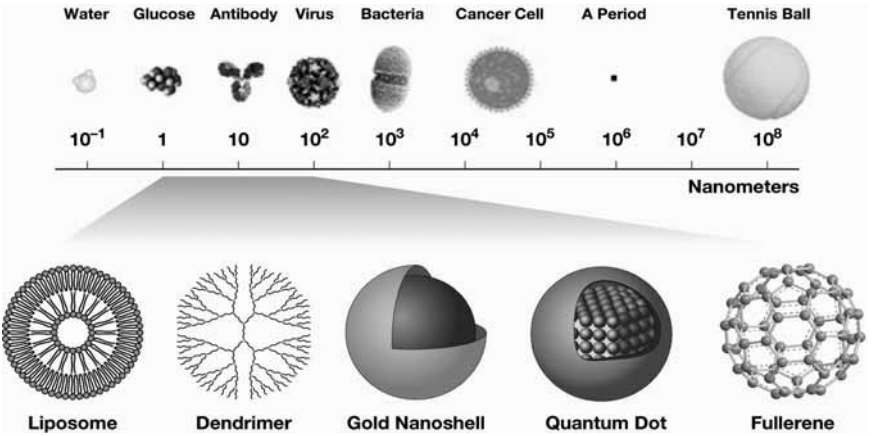


FIGURE 1 Comparison of size of objects relative to a nanometer. Images on the bottom are examples of objects that often have sizes in the 1–100 nm range. SOURCES: Barker presentation (July 12, 2010) and NCI (2010b).

already on the market. Several of the first FDA-approved uses of nanotechnology in medicine were for new formulations of standard chemotherapeutic agents to enhance delivery of the drugs to cancer cells and reduce side effects suffered by patients. Researchers have also used nanotechnology to improve contrast materials for imaging tumors. Nanotechnology holds promise for diagnostic tools and multifunctional products such as theranostics, which combine diagnostic tests with therapeutic agents.

A great deal of research funding is currently being devoted to research in nanomedicine, providing ample opportunity for scientific advances and new products. Even so, there are substantial challenges to overcoming clinical research and translational science hurdles. These challenges include

- Bridging interdisciplinary gaps to gather basic knowledge in order to more effectively design, develop, test, and regulate nanomedicines
- Developing appropriate standards for testing, manufacturing, and regulation of nanotechnology, and closing current regulation gaps
- Discerning and balancing the risks and benefits of nanotechnology, as well as conveying these risks and benefits to both policymakers and the public.

To explore what nanomedicine is, what it can do, its potential risks and benefits, and the state of the art for standards and regulation, all with respect to nanomedicine in oncology, the National Cancer Policy Forum held a workshop in Washington, DC, on July 12–13, 2010, titled "Policy Issues in Nanotechnology and Oncology." This document is a summary of the workshop. The workshop discussions fell under several main categories: uses of nanotechnology in oncology and cancer research, research and development of new cancer nanomedicines, risk management, and nanotechnology and the public. These topics form the chapters of this summary; policy issues, such as regulation of nanotechnology-based products and the challenges of facilitating interdisciplinary education, research, and development are discussed as they arose in the workshop proceedings. The views expressed in this summary are those of the speakers and discussants, as attributed to them, and are not the consensus views of workshop participants of members of the National Cancer Policy Forum. Further information on nanomedicine and nanotechnology can be found by starting with reviews in the scientific literature (Boisselier and Astruc, 2009; Debbage, 2009; Gao et al., 2009; Kostarelos et al., 2009; Moghimi et al., 2005; Nie et al., 2007; Peer et al., 2007; Riehemann et al., 2009). This summary organizes the themes of discussion by topic, and topics and quotations are not necessarily arranged in chronological order.

WHAT ARE NANOTECHNOLOGY AND NANOMEDICINE?

Dr. Mauro Ferrari, president, chief executive officer and director of the Methodist Hospital Research Institute, began the workshop by pointing out that there are multiple operational definitions of nanotechnology in different agencies and countries. But the key features these definitions tend to all share are that nanotechnology is engineered materials that make use of the unique physical properties possessed by the materials due to their size—properties that blend atomic or molecular properties with more commonly encountered bulk properties. The unique properties of nanomaterials enable novel applications, but, as several speakers pointed out, require the harnessing of multiple disciplines, such as physics, chemistry, engineering, materials science, and biology to further the field of nanotechnology.

Dr. Ferrari used the term "nanomedicine" to broadly define the application of nanotechnology to medicine, which would include imaging applications. But others, as he pointed out, use the term nanomedicine to refer to specific therapeutic agents made with nanotechnology. Dr. King Li, senior member of the Methodist Hospital Research Institute, chair of the department of radiology at the Methodist Hospital, director of the molecular imaging program and professor of radiology at the Weill

Medical College of Cornell University added that "cancer nanomedicine is more than just the materials. I think we can achieve more if you think about it as a combination of materials science, focused energy [delivery], targeted drug delivery, and molecular biology all intersected in the middle. That is the direction that we are moving," he said. Others debated the definition of nanotechnology used for regulatory purposes. This debate will be covered in Chapter 5.

BOX 1
Nanomaterials Used in Medicine

Several different kinds of nanomaterials are used in diagnostics and therapeutics, including nanoparticles, nanoshells, quantum dots, nanowires, fullerenes, micelles, liposomes, and dendrimers. See below for descriptions of these nanomaterials.

Nanoparticles

In addition to many other uses, nanoparticles are nano-size particles used to target tumor and other cells of interest for imaging or treatment purposes. These particles are composed of a variety of materials and can be made to contain therapeutic molecules that they release when they bind to their target. The term nanoparticle generally refers to materials made from a wide variety of inorganic materials, such as metals, semiconductors, or oxides. Nanoparticles made from semiconductor materials, sometimes referred to as quantum dots, are also described in this box. Nanoparticles are also referred to as nanocrystals when the materials composing the particles are crystalline.

Nanoshells

These usually have a core of silica and a metallic outer layer and can be decorated with molecular probes for cancer-related compounds. Nanoshells can be used to image tumors and for theranostics. For the latter, energy is directed at a tumor site and selectively absorbed by the nanoshells that accumulate in tumor cells. The heat of the energized nanoshells kills the tumor cells. Nanoshells are also used to provide targeted delivery of drugs to tumor cells.

Quantum dots

The term "quantum dot" refers to nanoparticles made from semiconductor materials such as cadmium selenide surrounded by a shell of zinc sulfide. When linked to an antibody or other molecule capable of binding to a target of interest, quantum dots can be concentrated at target-rich areas in an organism or tissue sample. Because of the multitude of colors with which they can emit light, quantum dots can be combined to create assays capable of detecting multiple substances simultaneously.

PHYSICAL PROPERTIES OF NANOMATERIALS

Several speakers gave examples of nanomaterials (see Box 1) and the different physical properties that nanotechnology products have, including different kinetics, diffusion characteristics, aerosol dynamics, fluid dynamics, size, and surface to volume ratio. Dr. Anna Barker, former deputy director of the National Cancer Institute, noted that the increased

Nanowires

These are wires of metal, oxide, or semiconductor materials, and they possess diameters in the nanometer range. Lengths can be hundreds of nanometers to centimeters or longer. These are valued for both their structural and electronic properties.

Fullerenes

The best-known fullerene is C_{60}, also called a buckyball. C_{60} is 60 atoms of carbon with icosahedral symmetry, similar to that of soccer balls. Single-walled and multi-walled carbon nanotubes are tubes formed from graphitic carbon. Carbon nanotubes can possess diameters of only a few nanometers and lengths from the tens to hundreds of nanometers up into the millimeter range. Carbon nanotubes may be bundled together or used singly. Fullerenes have exceptional strength and unique electrical and thermal properties.

Micelles and Liposomes

Biomolecules can also be used as building blocks for nanomaterials. Sometimes referred to as nanoparticles, micelles and liposomes are particles made from lipids. Lipid molecules are hydrophilic on one end and hydrophobic on the other end. Micelles consist of single lipid layers arranged into a sphere. In aqueous solutions, the hydrophobic ends point towards the interior of the sphere, allowing hydrophobic molecules to be transported in aqueous solutions. In hydrophobic solutions, the hydrophilic ends point towards the interior of the sphere, allowing water soluble cargo. Liposomes are small particles constructed from lipid bilayers;if the hydrophilic end of the outer layer is pointing outward, then the hydrophilic ends of the interior layer are pointing inward. Like micelles, liposomes can carry molecules in their interior cavity; in aqueous solutions, cargo is generally water soluble. Lipidic structures such as micelles or liposomes may surround chemotherapeutic agents and passively accumulate in tumors, where they release their drugs, or they may be decorated with antibodies that target tumor-specific proteins.

Dendrimers

These are ordered, branched polymers. Dendrimers enable multiple functions to be achieved with a single nanoparticle as each branch can be designed to have a different nanomedicine or diagnostic component.

surface to volume ratio of some nanomaterials enables researchers to attach more components per unit volume. In addition, different types of molecules with differing targets can be attached to single nanoparticles. She added that their small size enables nanomaterials to easily enter most cells, where they can readily interact with biomolecules on both the cell surface and within the cell.

Dr. Joseph DeSimone, Chancellor's Eminent Professor of Chemistry at the University of North Carolina at Chapel Hill and William R. Kenan Jr. Distinguished Professor of Chemical Engineering at North Carolina State University, noted that size and shape influence the likelihood that particles will enter the cell via endocytosis. Nanoparticles, especially rod-shaped particles, are more likely to enter a cell by this process, he said. This is advantageous because endocytosis protects the particle's payload from being ejected by cellular pumps, which are known to confer drug resistance (Heath et al., 2009).

The size of nanomaterials can also be advantageous for targeting tumor cells. Nanomaterials are not so small that they are rapidly eliminated through the kidney, yet they are small enough that they are more likely to penetrate the leaky blood vessels that feed tumors and concentrate in tumor tissue, as opposed to normal tissue, many speakers pointed out. "The sweet spot for cancer applications is that just by the fact that particles are roughly a hundred nanometers in size; there's passive accumulation in tumors," said Dr. Scott McNeil, director of the Nanotechnology Characterization Laboratory.

Dr. DeSimone added that the inhalation properties of medicines are also strongly influenced by their size and shape. By engineering those properties on the nanoscale, one can acquire the aerodynamics needed to effectively deliver inhaled medicines deep into the lungs, his dog animal model suggests. There also can be sustained release and residence in certain tissues due to the unique features of various nanomaterials that other classic small molecules do not have, according to Dr. Barker.

Lastly, Dr. Scott Manalis, associate professor of biological and mechanical engineering at Massachusetts Institute of Technology, pointed out that the small size of nanomaterials such as cantilevers give them a greater sensitivity to mass. These microscopic, flexible beams can provide rapid and sensitive detection of altered weight and other traits of individual cells. In addition, cantilevers can be coated with genetic or other molecular probes for cancer-related molecules. When target molecules in solution bind to the cantilever-bound probes, bending of the cantilevers occurs, which triggers an electrical or visual signal that can be detected. How cells differ in weight may have diagnostic or prognostic significance in cancer, which alters cell growth rates, he said (see also Box 2).

The unique properties of nanomaterials will influence the tests used

BOX 2
Single-Cell Diagnostics

Drs. James Heath, Elizabeth W. Gilloon Professor and professor of chemistry at the California Institute of Technology, professor of molecular and medical pharmacology at the University of California, Los Angeles, and director of the NanoSystems Biology Cancer Center, and Scott Manalis, associate professor of biological and mechanical engineering at Massachusetts Institute of Technology, showed how it is possible to do single-cell diagnostics using nanotechnology. Dr. Heath uses his barcode nanotechnology, as described previously, to detect as many as 20 cancer-triggering P13K pathway proteins from single cells. "Out of this type of analysis, one can develop a network of the system," he said.

Such single-cell analyses are revealing some unexpected findings that were not previously discovered using microarray technology on multiple cells, and may be able to counteract the misinterpretations that arise when multiple heterogeneous cancer cells are combined in a single analysis, generating average results that misrepresent the more diverse results found in the sample. For example, some cells may have high amounts of epidermal growth factor (EGF) and erlotinib, which targets EGF, while others have low amounts of the growth factor and this drug that targets it. By mixing these cells in a single analysis, one may miss a correlation between having high amounts of EGF and also having high amounts of erlotinib because the average of these cells does not indicate this correlation.

In his lab, Dr. Manalis has been pursuing single-cell assessments of physical properties such as mass, weight, and density. "It should be useful to measure these types of parameters, not only to understand cancer and its disregulation of the cell cycle and cell growth, but also how cells respond to drugs that can be ultimately used to predict which therapies are likely to work in patients," he said.

He has used cantilevers with U-shaped channels for fluid flow to determine the mass of single cells. With this setup, he has dramatically increased the ability to measure mass over conventional methods. The smaller the cantilevers, the better the resolution. "Not only can we weigh a single cell, but we can weigh it with a precision that is about a thousand times less than the cell itself. So we can measure very, very small changes in the weight of the cell," Dr. Manalis said.

Dr. Manalis has also developed similar nanodevices that weigh single cells in two different fluids to determine the density of individual cells. Using these measurements, he has been able to show differences between red blood cells from anemic versus normal individuals, and to discern actively dividing lymphoblasts from normal white blood cells.

He also has developed a way to pause cells in transit in his devices so their weight and density can be measured repeatedly over time. Using this method, he is currently assessing the effects of various treatments on the weight and density of individual cancer cells, which are measured before and after the treatment. He is also using fluorescent tags for stages of the cell cycle while simultaneously measuring mass or density. "We envision this as a way to study how density and mass [as indicators of cell growth] are perturbed by giving cells drugs at different parts of the cell cycle," Dr. Manalis said.

to characterize them, both Drs. McNeil and Yuliang Zhao pointed out. "Very naively we thought five and six years ago that we could simply take an off-the-shelf kit and characterize nanomaterials, and that's not the case. [The nanomaterials] will interfere with the assay—many nanoparticles will absorb at the same wavelength that the colorimetric assays do. Some particles are catalytic and will cleave a substrate so you get false positives," said Dr. McNeil. Dr. Yuliang Zhao, director of the Chinese Academy of Sciences' Key Lab for Nanosafety added that additional parameters are required when characterizing the toxicity of nanomaterials, besides mass concentration, reactivity, solubility and other standard parameters. These additional parameters include quantum effects, structure, shape, particle concentration, number, size, size distribution, surface chemistry, and tendency to aggregate or self assemble.

2

Uses of Nanotechnology in Oncology and Cancer Research

One of the ways that scientists are working to overcome the shortcomings of current cancer diagnostics and treatments is through the use of nanotechnology, Dr. Barker explained. This chapter demonstrates current uses of nanotechnology in oncology and cancer research as presented by workshop speakers. In turn, diagnosis and monitoring, treatment, prevention, and clinical uses are discussed.

Genetic research has revealed that tumors are not only heterogeneous, but they continue to change with time, she said. For example, the brain tumor glioblastoma multiforme is treated as a single type of cancer, but recent research done by The Cancer Genome Atlas has revealed that there are at least four subtypes of this kind of cancer, and numerous subtypes are being discovered for ovarian and other cancers. The genetic expression of cancers also tends to change as they progress. "As important in understanding what the genome looks like, is how the genome is expressed in space over time as this is really important when you start thinking about delivering agents," she said (see Figure 2).

Tumors also have numerous traits that make their effective treatment daunting, Dr. Barker pointed out. These traits include self-sufficiency in growth signals, the ability to evade programmed cell death and induce immunologic tolerance, limitless potential to replicate, and the ability to invade tissues and form metastases that can induce the growth of blood vessels to support them.

"If you understand what cancer fundamentally is, what you come to fairly quickly is that we are totally underpowered in terms of being

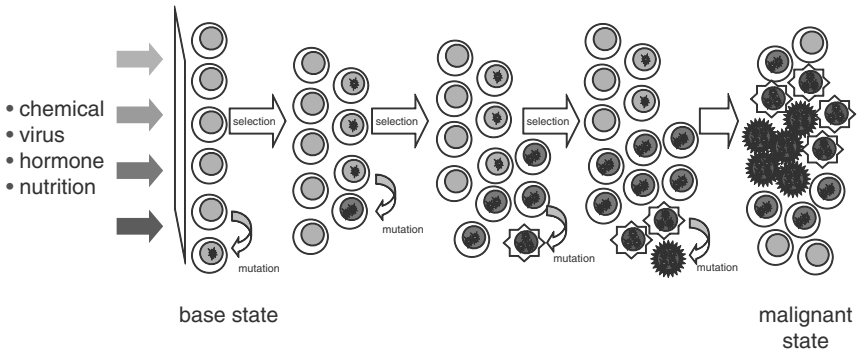


FIGURE 2 Cancer is a complex, evolving system involving chemical, viral, hormonal, and nutritional inputs. Over time, mutation and selection can lead to a malignant state, but there is insufficient biological understanding of these processes over time, according to Dr. Barker.
SOURCE: Barker presentation (July 12, 2010).

able to capture and deliver the kind of information [needed to effectively diagnose and treat cancer] in any of the technologies we currently use, including our chip technologies, because there is a lot of information being managed by cancer when it takes over a normal [biologic] process," Dr. Barker said.

Nanotechnology has the capacity to deal with the complexity of cancer, she said, by providing tools that can help elucidate what drives cancer initiation and progression; providing tools that can help define the types and subtypes of cancer and combining measurement of cancer biomarkers that can diagnose cancer with therapies that target the specific disease identified by diagnostic measurements; capturing enough information to diagnose cancer at the earliest possible time; for established disease, defining therapeutic targets and directing agents to those target while sparing normal cells; monitoring the effectiveness of an intervention; and sensing pre-neoplastic changes that may benefit from preventive therapy.

"I see nanotechnology as an enabler of pretty much everything we want to do in terms of delivering information to cancer cells, getting information from cancer cells, and combining what we know about normal cells and what we know about cancer cells to be able to differentiate them," Dr. Barker said.

Dr. Barker then elaborated, as did others, on what nanotechnology is doing or has the potential to do for the diagnosis, monitoring, treatment, and prevention of cancer.

DIAGNOSIS AND MONITORING

To diagnose cancer, physicians rely on imaging that reveals tumors or their linked tissue abnormalities. The detection limit for tumors depends, in part, on the selectivity and the signaling capacity of the contrast material that is used to make them apparent. Increasingly, cancer diagnosis also depends on molecular tests that can discern genes or proteins that are present in abnormal levels. Speakers at the workshop showed how nanotechnology has the potential for improving the diagnosis and monitoring of cancer by enabling high-throughput detection of complex molecular signatures and by enhancing imaging contrast.

Molecular Signatures

Much of modern cancer diagnostics that underlies the new "personalized medicine" approach being taken on the forefront of oncology depends on deciphering complex molecular signatures from blood or tumor samples. But, as Dr. Ferrari pointed out, detecting such cancer-linked molecular signatures in blood is like detecting a needle in a haystack because within a single drop of blood, there can be upward of a million different compounds. Adding to this challenge is the fact that enzymes in blood rapidly degrade the proteins present in a blood sample.

Dr. Ferrari then showed how this challenge is being met by various nanotechnologies, including one developed in his laboratory. In collaboration with Dr. Zhao, Dr. Ferrari has developed silicon chips that are engineered on the nanoscale to have a textured surface with micropores that can separate out proteins by size and charge (see Figure 3). Researchers can use these nanochips to do high-throughput separation of the low molecular weight components of blood proteins from other compounds in a blood sample. This not only enriches the less abundant but more diagnostically significant components of a blood sample, which can later be analyzed using mass spectroscopy, but it eliminates the enzymes that degrade the sample (Sakamoto et al., 2010).

"By taking out all of those compounds that you do not want, it is like taking the sun out of the sky; all of a sudden you can see the stars and it is very facile and quick—it literally takes seconds to perform," Dr. Ferrari said.

Dr. Barker added that nanotechnology offers opportunities for unprecedented levels of sensitivity and breadth of information, with "bio-barcode" technologies able to detect as little as one molecule of interest in a drop of blood as well as to simultaneously measure hundreds of proteins (see Table 1). "This is an extraordinary leap forward for what we can do with diagnostics, in terms of the numbers of parameters we can

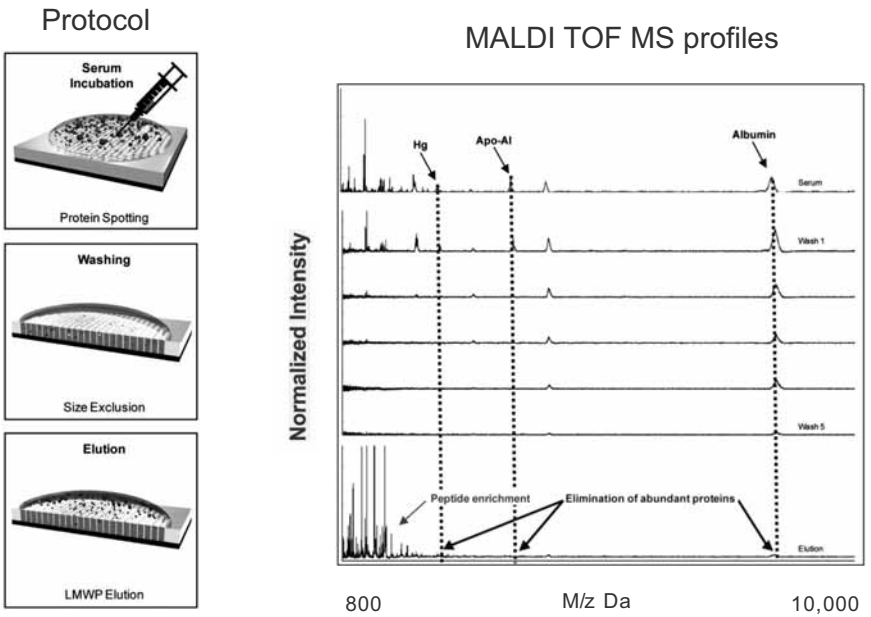


FIGURE 3 Nanotechonology can aid in the development of targeted diagnostics. For example, nanoporous silica films can aide in the identification of molecular signatures through high-throughput separation of low molecular weight components of blood proteins from other compounds in a blood sample.
NOTES: Apo-A1 = apolipoprotein A1; Hg = mercury; LMWP = low molecular weight peptide; MALDI TOF MS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.
SOURCE: Ferrari presentation (July 12, 2010).

measure. It potentially gives us, for the first time, the chance to measure [protein] signatures, which is a really big step forward," said Dr. Barker.

The barcode technologies sieve blood through nano-size channels on chips as small as four centimeters wide. The channels separate the plasma that contains cancer-linked proteins from the blood cells and let it flow down narrower channels that contain an array of bars coated with antibodies or other molecular probes. Each probe will bind to only a specific protein, and fluorescent tags for such binding cause a barcode to light up that indicates the blood's protein signature (Heath et al., 2009) (see Figure 4).

Researchers tested the ability of this barcode to detect prostate-specific antigen (PSA), which is used to monitor prostate cancers, and found that it could detect minute changes in PSA that were not detected in standard PSA assays.

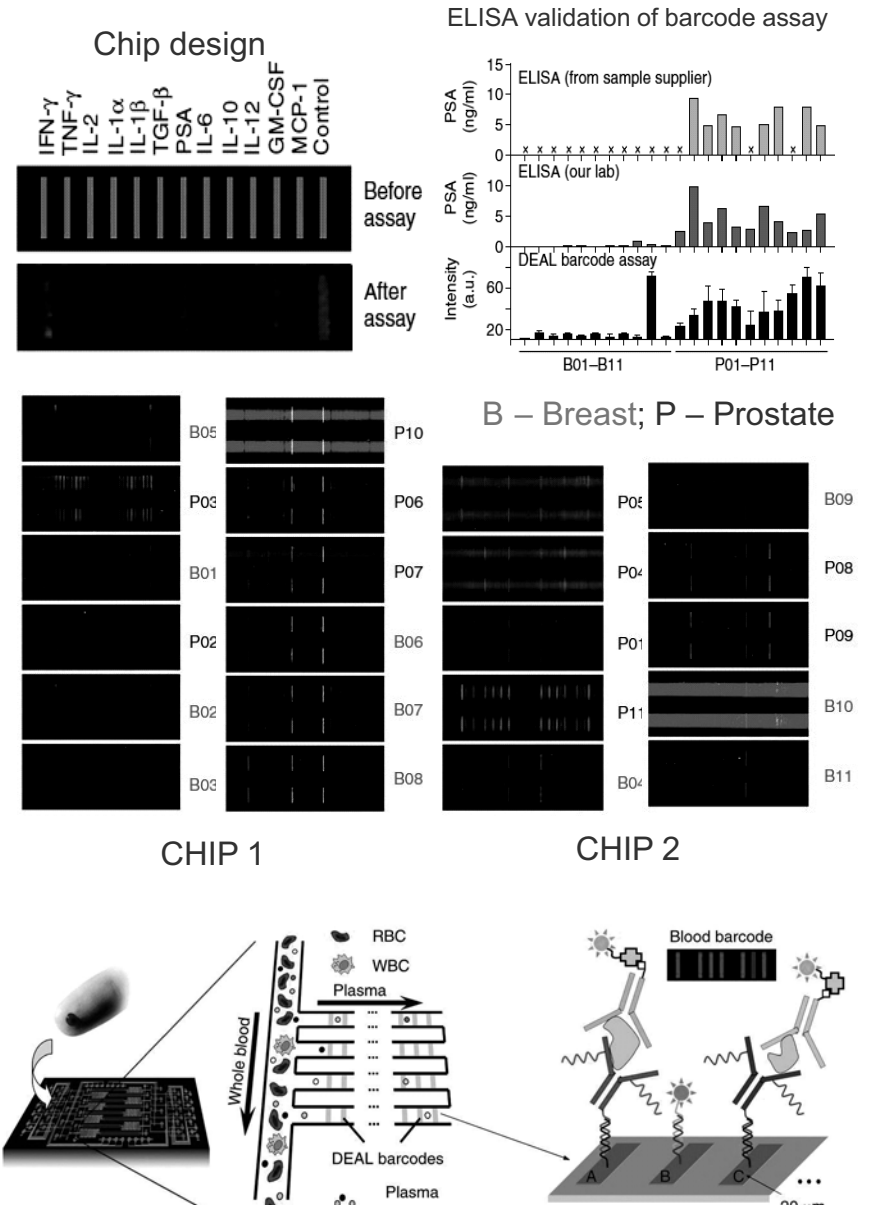
TABLE 1 Biomolecule Detection Technology

Concentration	Molecules per Drop	Detection Methods and Targets/Diseases
10^{-3} – Millimolar	Quadrillions	Colorimetric/Enzymatic Chemistry Blood Sugar (Diabetes)
10^{-6} – Micromolar 10^{-9} – Nanomolar 10^{-12} – Picomolar	Trillions Billions Millions	ELISA and Chemiluminescence Troponin, CK-MB, BNP, βhCG
10^{-15} – Femtomolar 10^{-18} – Attomolar 10^{-21} – Zeptomolar	Thousands Tens <1	Bio-barcode technologies Cancer: prostate, ovarian, breast Alzheimer disease, mad cow disease, pulmonary disease, cardiovascular disease

NOTES: Nanotechnology offers opportunities for unprecedented levels of sensitivity for high content diagnostics. βhCG = β subunit of human chorionic gonadotropin; BNP = brain natriuretic peptide; CK-MB = creatine kinase MB fraction (the MB fraction is most specific to cardiac muscle); ELISA = enzyme-linked immunosorbent assay.
SOURCE: Barker presentation (July 12, 2010).

"These barcode technologies are really going to set the stage for early detection and are also driving the power of functional imaging of targets, which is one of the earlier wins in the clinic," Dr. Barker said. "With this technology you can also think about prevention, which we haven't been able to do in the past." Dr. Ernie Hawk, vice president and division head for cancer prevention and population sciences at MD Anderson Cancer Center, added that "nanotechnology offers the potential to improve our ability to detect early-stage disease or to assay its progression," but he noted that it remains to be seen whether nanotechnology screening devices will have the sensitivity and specificity to detect a small collection of cells on a neoplastic pathway.

Barcode technology is likely to be useful in monitoring response to cancer therapies. Dr. James Heath, Elizabeth W. Gilloon Professor and professor of chemistry at the California Institute of Technology, professor of molecular and medical pharmacology at the University of California, Los Angeles, and director of the NanoSystems Biology Cancer Center, showed how his barcode technology was able to reveal, over time, changes in key melanoma-linked proteins in patients undergoing T-cell immunotherapy. These patients just had to provide a pinprick of blood daily for the researchers to capture the change in the dynamic evolution of their protein signatures during the course of therapy.


Chip design
IFN-γ
TNF-γ
IL-2
IL-1α
IL-1β
TGF-β
PSA
IL-6
IL-10
IL-12
GM-CSF
MCP-1
Control
Before assay
After assay
ELISA validation of barcode assay
ELISA (from sample supplier)
ELISA (our lab)
DEAL barcode assay
PSA (ng/ml)
Intensity (a.u.)
B01–B11
P01–P11
B – Breast; P – Prostate
B05
P03
B01
P02
B02
B03
P10
P06
P07
B06
B07
B08
P05
P04
P01
P11
B04
B09
P08
P09
B10
B11
CHIP 1
CHIP 2
RBC
WBC
Plasma
Whole blood
DEAL barcodes
Plasma proteins
Blood barcode
A
B
C
20 μm

Enhanced Contrast

Nanotechnology holds promise in improving diagnostic imaging by enhancing the contrast used to do the imaging. "Imaging is one of our earliest wins already," said Dr. Barker. "We work with places like General Electric and other industries that are using nanotechnology to change everything they are doing about imaging. I think it is going to continue to … change imaging in the years to come."

Dr. Lee Josephson, associate professor in the Department of Radiology at Harvard Medical School and associate professor with the Center for Translational Nuclear Medicine and Molecular Imaging at Massachusetts General Hospital, showed how magnetic iron-based nanoparticles with fluorescent tags can act as enhanced magnetic resonance (MR) contrast agents and be used for MR-based assays. These nanoparticles can be targeted to tumors by attaching probes for compounds linked to certain cancers, or they can target normal tissue by having probes for receptors found only on normal cells.

Magneto–fluorescent nanoparticles (MFNP) have two main advantages over standard MR contrast agents, according to Dr. Josephson. The magnetic and crystalline nature of these particles heightens their ability to be detected in MR scans. In addition, unlike many fluorescent chelates and dyes conventionally used for contrast, MFNP are internalized by cells

FIGURE 4 In vitro diagnosis and post-therapy monitoring using large-scale, multi-parameter protein analysis in microfluidic devices. (top) Multiplexed protein measurements of clinical patient sera for prostate and breast cancers. The integrated blood barcode chip (IBBC) is used to measure the cancer marker PSA and 11 cytokines from 22 cancer patient serum samples. B01–B11 are samples from breast cancer patients; P01–P11 are samples from prostate cancer patients. (bottom) The IBBC method: plasma is separated from a finger prick of blood using multiple DNA-encoded antibody barcode (DEAL) arrays patterned within microfluidic plasma-skimming channels for multiplex fluorescence detection.
NOTES: B = breast cancer; DEAL = DNA-encoded antibody barcode; GM-CSF = granulocyte-macrophage colony stimulating factor; IBBC = integrated blood barcode chip; IFN-γ = interferon-γ; IL-1α = interleukin-1α; IL-1β = interleukin-1β; IL-2 = interleukin-2; IL-6 = interleukin-6; IL-10 = interleukin-10; IL-12 = interleukin-12; MCP-1 = monocyte chemotactic protein-1; P = prostate cancer; PSA = prostate-specific antigen; RBC = red blood cell; TGF-β = transforming growth factor β; TNF-γ = tumor necrosis factor γ; WBC = white blood cell.
SOURCES: Barker presentation (July 12, 2010) and Fan et al. (2008). Adapted by permission from Macmillan Publishers Ltd: *Nature Biotechnology* 26(12):1373–1378, copyright 2008.

and are not rapidly metabolized, so they are retained long enough that they can be used for both pre-surgery imaging, as well as during surgery (intravital) to detect tumor margins (see Figure 5).

"If you inject MFNP 6 or even 12 hours prior to an operation, you will be able to see where they are intraoperatively," Dr. Josephson said.

Dr. Kristen Kulinowski, senior faculty fellow in the Department of

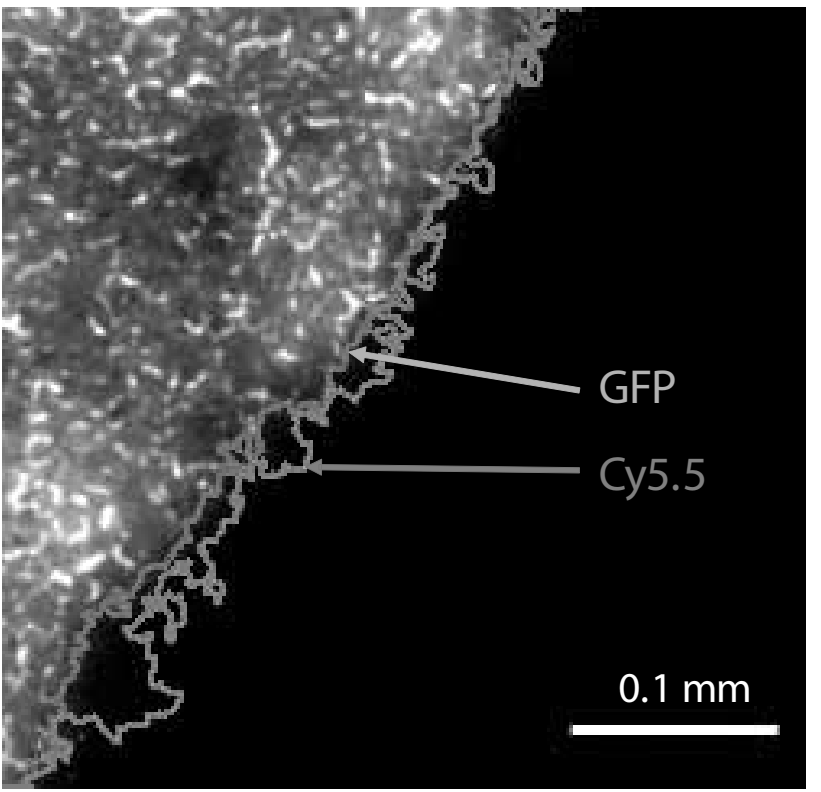


FIGURE 5 Measurement of nanoparticle fluorescence to determine tumor margin. The Cy5.5-labeled nanoparticles were injected in the mouse model prior to surgery and were used as a contrast agent for magnetic resonance imaging. Images like the one above can then be taken intraoperatively for use in tumor border determination. This image compares tumor border determination using CLIO-Cy5.5 and green fluorescent protein (GFP). The tumor border was determined using signal intensity measurements.

NOTE: CLIO-Cy5.5 = cross-linked iron oxide–Cy5.5.

SOURCES: Josephson presentation (July 12, 2010) and Trehin et al. (2006). Reprinted, with permission, from *Neoplasia*, 2006. Copyright 2006 by Neoplasia Press.

Chemistry at Rice University and Director for External Affairs for the Center for Biological and Environmental Nanotechnology, added that researchers at Rice University have already started clinical trials using silica–gold nanoshells as real-time molecular probes for breast tissue that overexpresses the breast cancer biomarker HER2. The nanoshells are added to tissue slices removed during breast cancer excision surgery and within 5 minutes can be detected with an optical imaging system (Bickford et al., 2010). "All this could be done very rapidly while the patient was still on the operating table, rather than having to rely on post-operative follow-up and retreatment," Dr. Kulinowski said. Dr. Josephson is currently exploring MFNP for measuring, during surgical removal of tumors, biomarkers that indicate the aggressiveness of cancer. "The idea is to look in aspirates of tumors for various biomarkers, such as growth factors, that would help the surgeon decide intraoperatively how aggressive is the cancer, instead of waiting for the report," he said.

Dr. Steven Curley, professor of surgery, chief of gastrointestinal tumor surgery, and program director of multidisciplinary gastrointestinal care at MD Anderson Cancer Center, pointed out that gadolinium-loaded carbon nanostructures or gold-coated nanoparticles also can be used as contrast agents for MR and provide more detail than standard contrast agents. "The imaging characteristics and the ability to see things on a much finer scale will definitely be enhanced [with these nanoparticles]," he said.

Another advantage to gold nanoparticles is that they can be used to both diagnose and treat tumors. This is an example of theranostics, and it can be done by first using the particles to target the tumors, and then applying a selective energy source, such as a laser, that is readily absorbed by the gold nanoparticles but not by normal tissues. The heat created by that absorption kills the tumor cells.

In his studies, Dr. Curley found that even at very low concentrations, gold nanoparticles produce significant levels of heat when exposed to a very focused radiofrequency field. The production of heat by the exposed nanoparticles was not only concentration dependent, but also size dependent, with smaller nanoparticles leading to faster heating rates, given a constant volume fraction of gold, Dr. Curley reported. He was able to completely control the tumors in animal models using this nanotechnology, without damage to their normal tissues. "This has the potential to be a targeted therapy with few if any side effects," he said. He added that investigators at Rice are currently using a similar thermal treatment using gold-coated nanoshells to treat oropharyngeal cancer in a clinical trial.

MR imaging using nanoparticles for contrast can also be done to do imaging assays of blood or other solutions. The advantage of this assay method stems from the penetrating radiofrequencies used in MR. "It allows us to have molecular readouts from solutions that are completely

refractory to light," Dr. Josephson said. "You can't do this with an ELISA or with fluorescent assays."

Another advantage of doing MR assays is that the assay can be interrogated with different pulse sequences, so one can assay for more than one variable. MR assaying systems have been developed that are compact, inexpensive, and portable. One micro MR imager can image ten microliter wells simultaneously, Dr. Josephson reported, and is about the size of an old cell phone. No separations are needed to do the imaging, and it can detect all kinds of molecular targets and correct for unknown reagent concentrations and viscosity.

Dr. Josephson also discussed MR nanosensors. In collaboration with Michael Cima at MIT, Dr. Josephson developed a nanosensor for human chorionic gonadotrophin (hCG), which is produced by some tumors. The sensor detects the aggregation of particles caused by the binding of the hCG probe. The sensors have some of the same advantages as the MR assays—they can detect multiple compounds with simple instrumentation, and, particularly relevant to sensors, they emit penetrating radiofrequency radiation, but have no power supply.

"In other words, what is implanted in the animal has no battery. The energy comes from the external NMR," Dr. Josephson said. This would enable the sensor to be implanted in an animal to detect substances released by tumors. He added that unlike blood tests that measure a cancer biomarker at a single moment in time, implantable sensors could measure the concentration of various biomarkers over time.

Quantum dots are another type of nanomaterial with versatile properties. Dr. Curley noted that quantum dots can function as optical imaging agents both for in vitro and in vivo blood testing, to track molecules, to show lymph node involvement for various cancers, and to image recurrent or residual infectious diseases.

TREATMENT

Several speakers showed how nanotechnology is likely to improve cancer treatment by improving its targeting precision. Many cancer drugs cause serious and sometimes fatal side effects because they are spread systemically throughout the body, where they do damage to healthy tissues. Such damage can be limited by more specific targeting to tumor cells.

The targeting can be passive and due to the physical properties of nanomaterials that enable them to penetrate tumor cells from the bloodstream, as previously described, or be active targeting due to being decorated with antibodies or other compounds that cause them to selectively bind to tumor cells. Selectivity can also be achieved by drugs encased in

nanoparticles that do not release their contents until they penetrate tumor cells.

Nanomedicines already on the market to treat breast or ovarian cancer do such specific targeting by encasing the conventional cytotoxic cancer drugs, such as Taxol, in albumin or liposomes, which are designed not to release their toxic contents until they enter tumor cells, thereby shielding healthy cells from their toxic effects. Dr. Neil Desai, senior vice president for global research and development at Abraxis Bioscience, reported that clinical trials of Abraxane, which is Taxol encased in albumin nanoparticles, found that that the maximum tolerated dose was about twice that for Taxol alone, and that breast cancer response rates of Abraxane were double that of Taxol. The drug was approved to treat breast cancer in 2005 and has since been shown in clinical trials to be an effective treatment for patients with pancreatic or lung cancers, or melanoma.

Researchers are also pursuing other nanoconstructs that shield healthy tissue from their toxic contents. Dr. DeSimone noted that his lab had created what he called "Trojan horse" nanoparticles that are pH-sensitive and chemically constructed to breakdown only in the intracellular environment. Such breakdown triggers the release of the drugs they carry.

Other nanoparticles have shown to be so selectively taken up by tumor cells, by both passive and active means, such that researchers can use higher and more effective doses of the cancer drugs they contain. For example, tumor necrosis factor (TNF) had been shown effective as a cancer treatment in limited limb perfusions, but had to be abandoned as a systemic treatment because of toxic reactions to the high enough doses needed to be effective. But with the advent of nanoparticles that are selectively taken up by tumor tissues, as opposed to healthy tissues, larger doses can now be safely used systemically, Dr. Steven Libutti, director of the Montefiore–Einstein Center for Cancer Care and professor and vice chair of surgery at Albert Einstein College of Medicine at Yeshiva University, reported. His research showed that he was able to safely administer tumor necrosis factor delivered via gold nanoparticles to melanoma patients at what was previously considered to be a lethal dose level of the compound (twice the LD50).

Consequently, reformulation of discontinued drugs is a growing area of nanomedicine development, Dr. McNeil noted. "Big pharma can produce tens of thousands, if not hundreds of thousands, of new chemical entities by medicinal chemistry," he said. "By far, the majority of those have to be disqualified due to insolubility or toxicity and so forth. So something that has been postulated is that nanotechnology might be able to resurrect some of those drugs, because we can truly engineer properties into and out of that formulation."

Nanomedicines have also been developed that not only specifically

target tumor cells, but the cancer-promoting genes they contain as well. Clinical trials of a nanomedicine that target specific RNAs are already underway, Dr. Barker pointed out. This nanoparticle contains silencing RNA that penetrates tumor cells via endocytosis (Davis et al., 2010).

Researchers can also create nanoparticles that have bigger payloads—multiple drugs, each with a different target, or drugs combined with agents that enhance their effectiveness. Nanoparticles can also have multiple functions. Some combine drugs with contrast agents, while others might someday be engineered to treat, monitor the effectiveness of treatment, and then re-treat if the treatment is not working, Dr. Barker noted. Dr. Li added that researchers also envision engineering "remote controlled drugs" that can be released or activated only when needed.

Nanotechnology has immense potential to further personalized medicine—defined as the use of new molecular technologies to get the right treatments to the right patients at the right time—many speakers noted. Dr. Ferrari pointed out that by using nanoparticles, researchers can personalize vectors not just to the patient but to the specific type of lesion the patient has, down to the subcellular level, in terms of which organelles it targets or which sections of RNA or DNA. This specialized targeting is "built into the physics and chemistry of the particles," he said, which can also determine both where and when therapeutic drugs are released.

Dr. Barker noted that the multiplexing capabilities of nanomedicines offers the possibility of targeting the many and diverse genetic defects that underlie specific cancers, as well as combining lesion detection with drug delivery and monitoring of the drug's effectiveness. "Personalizing means getting the bioactive molecules that you want at the right place at the right time, finding out whether they work pretty quickly, and engaging the biology into some sort of a natural healing process that is better than was present before the administration of the nano drug," Dr. Ferrari added.

Dr. Barker concurred adding, "We're developing a field that is actually looking at the interplay of whatever we're administering with the cells that we're interested in. And we're doing that in ways we never did before. Why is that? It's because we have the capability of nanostructures to do that. Right now we throw some small molecules into circulation and hope they get there, and generally they don't. So I think this is an area where if you functionalize these particles and have the right delivery vehicle, you [can do better]," Dr. Barker said.

But Dr. Ferrari cautioned against overdecorating nanoparticles with compounds that target specific tumor cells or making their payloads too extensive because the more complex nanoparticles become, the less likely they may be to overcome the biological barriers that can prevent

them from reaching their targets. This concept is discussed further in the section Design Complexity of Nanomaterials for Medical Applications in Chapter 3.

PREVENTION

Many of the advantages nanotechnology provide for treatment and diagnostics are likely to be also relevant to the prevention of cancer, Dr. Hawk pointed out, including the ability to have larger payloads and deliver a combination of agents. Studies (McLaren et al., 2008; Meyskens et al., 2008) show that two compounds, such as DFMO (difluoromethylornithine) and Sulindac, can be more effective than either agent alone at reducing colon cancer recurrence, he said. "This and a great deal of other clinical work leads me to believe that using nanotechnology as a combinatorial platform will be as relevant to prevention as it is in therapy," Dr. Hawk stressed.

But does the leakiness of tumor blood vessels, which enables passive transport of nanomaterials into cancer cells, occur in preinvasive lesions, and thus become relevant to prevention efforts using nanoparticles? This is not known yet, but is actively being explored, Dr. Hawk reported. Such selective targeting would be an advantage for compounds such as epigallocatechin-3-gallate (EGCG), which is found in green tea and appears to have some cancer-preventing properties, but has poor oral absorption, with few people consuming green tea in high enough quantities to reap the compound's cancer-preventing benefits.

One research lab at the University of Wisconsin created a nanoparticle that could deliver high doses of EGCG. They found, in an animal model, that there was efficient uptake of the nano-delivered EGCG by prostate cancer cells, where it induced programmed cell death, inhibited the formation of blood vessels, and decreased tumor volume (Siddiqui et al., 2009). In addition, the nanoEGCG was as effective as a tenfold higher dose of EGCG delivered by standard means in a mouse xenograft model using prostate cancer cells (Siddiqui et al., 2009).

Researchers are also currently developing nano versions of nonsteroidal anti-inflammatory drugs (NSAIDs) that could mitigate the adverse effects of these drugs without compromising their protective properties, which include preventing gastric cancers of the gastrointestinal tract, Dr. Hawk added.

"Are we there yet in terms of nanotechnology impacting cancer prevention? I don't think so. However, there are very important endeavors underway right now to try to expand the potential usefulness of this exciting technology in screening and prevention," Dr. Hawk concluded.

NANOTECHNOLOGY IN THE CLINIC

Although many of the applications of nanomedicine described at the workshop are in preclinical stages, and some are still in proof-of-principle stages, several participants stressed that nanotechnology is already being applied to the clinic.

"Nanotechnology is a very real field. It is not science fiction, a 'let's see what happens in the future' type of field," Dr. Ferrari said. He pointed out that one of the first nanomedicines—the liposomal cancer medicine Doxil—has been used in the clinic for over 15 years, and in addition to the dozens of different nanotechnology approaches that are currently being tested, many clinical trials are testing agents that have already been approved, such as liposomes with doxorubicin in combination with other drugs.

During his presentations, Dr. Li showed a list of two dozen either approved nanotechnology cancer drugs or potential nanotechnology cancer drugs currently in clinical trials, which he said was just a partial list of all the nanomaterials being used in the clinic, and did not include Dr. Libutti's nanoTNF, which is currently being tested in a clinical trial (see Table 2). In addition, Dr. Barker listed one nanotechnology imaging agent that has conditional FDA approval (iron oxide nanoparticles) and one in preclinical development (PAMAM dendrimers for MRI imaging).

TABLE 2 A Partial List of Nanotechnology Drugs Currently in Clinical Trials

Compound	Name	Indication	Status
Liposomal doxorubicin	Myocet, Caelyx (Doxil)	Breast, ovarian, KS	Approved
Liposomal daunorubicin	Daunoxome	Kaposi sarcoma	Approved
Liposomal vincristine	Onco-TCS	Non-hodgkin lymphoma	Approved
Liposomal cisplatin	SPI-77	Lung	Phase II
Liposomal lurtotecan	OSI-211	Ovarian	Phase II
Cationic liposomal c-Raf AON	LErafAON	Various	Phase I/II
Cationic liposomal E1A pDNA	PLD-E1A	Breast, ovarian	Phase I/II
Thermosensitive liposomal doxorubicin	ThermoDox	Breast, liver	Phase I
Albumin-paclitaxel	Abraxane	Breast	Approved
Albumin-methotrexate	MTX-HSA	Kidney	Phase II
Dextran-doxorubicin	DOX-OXD	Various	Phase I
PEG-L-asparaginase	Oncaspar	Leukemia	Approved
PEG-IFN2a/-IFN2b	PegAsys/ PegIntron	Melanoma, leukemia	Phase I/II
PHPMA-doxorubicin	PK1	Breast, lung, colon	Phase II
Galactosamine-targeted PK1	PK2	Liver	Phase I/II
PGA-paclitaxel	Xyotax	Lung, ovarian	Phase III
Paclitaxel-containing polymeric micelles	Genexol-PM	Breast, lung	Phase II
Cisplatin-containing polymeric micelles	Nanoplatin	Various	Phase I
Doxorubicin-containing polymeric micelles	NK911	Various	Phase I
SN38-containing polymeric micelles	LE-SN38	Colon, colorectal	Phase I
^{90}Yttrium-Ibritumomab tiuxetan (α-CD20)	Zevalin	Non-hodgkin lymphoma	Approved
DTA-IL2 fusion protein (α-CD25)	Ontak	T-cell lymphoma	Approved

continued

TABLE 2 Continued

Compound	Name	Indication	Status
Ozogamycin-gemtuzumab (α-CD33)	Mylotarg	Leukaemia	Approved
Doxorubicin-cBR96 (α-CD174)	SGN-15	Lung, prostate, breast	Phase II

NOTES: α-CD20 = anti-CD20, CD20 is cluster of differentiation 20, a cell surface protein; α-CD33 = anti-CD33, CD33 is cluster of differentiation 33; DOX-OXD = dextran conjugated doxorubicin; Doxorubicin-cBR96 (α-CD174) = doxorubicin conjugated to chimeric monoclonal antibody cBR96 (anti-CD174, CD174 is cluster of differentiation 174, a cell surface protein); DTA-IL2 fusion protein (α-CD25) = fusion protein of diphtheria toxin fragment A and interleukin 2 (this fusion protein targets CD25, a cell surface protein); Genexol-PM = Genexol–polymeric micelle; KS = Kaposi sarcoma; LE-SN38 = liposome-encapsulated 7-Ethyl-10-hydroxy-camptothecin; LErafAON = liposome encapsulated c-raf antisense oligonucleotide; MTX-HSA = human serum albumin–bound methotrexate; NK911 = polymeric micelle carrier system for doxorubicin; Onco-TCS = Onco-transmembrane carrier system, the drug vincristine; OSI-211 = liposomal lurtotecan drug manufactured by OSI Pharmaceuticals; PEG-IFNα2a/-IFNα2b = pegylated interferon α-2a/interferon α-2b; PEG-L-asparaginase = polyethylene glycol conjugated asparaginase; PGA-paclitaxel = polyglutamic acid conjugated paclitaxel; PHPMA-doxorubicin = poly(2-hydroxypropyl methacrylate) conjugated doxorubicin; PK1 = N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin; PK2 = N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer backbone and pendant doxorubicin (DOX) linked via a Gly-Phe-Leu-Gly peptide spacer; PLD-E1A = pegylated liposomal doxorubicin–linked E1A (an adenoviral oncogene) plasmid DNA; SGN-15 = cBR96-doxorubicin (see above) immunoconjugate, SGN stands for Seattle Genetics Inc.; SPI-77 = sterically stabilised liposomal cisplatin.

SOURCES: Li presentation (July 12, 2010) and Lammers et al. (2008). Reprinted by permission from Macmillan Publishers Ltd: *British Journal of Cancer* 99(3), copyright 2008.

3

Research and Development of New Cancer Nanomedicines—Challenges and Solutions

Although much progress has been made in applying nanotechnology to medicine, in order to effectively design, develop, test, and regulate nanoproducts, more needs to be understood about nanomaterials, including their stability, what biological barriers they are able to cross, how best to predict and track their biodistribution, how best to assess their toxicity, and how effective and reliable is their cancer targeting.

Much needs to be done to improve the design and development of nanomedicines, including designing nanomedicines that are more clinically relevant and translatable, improving the scale up and quality control of nanomaterials, developing inexpensive molecular probes that can be manufactured more reliably than antibodies, and developing prevention nanotherapies that can be administered orally. This chapter discusses challenges in basic biology (including biomarker discovery), strategies for improving nanoparticle targeting effectiveness and efficiency, design complexity of nanomaterials for medical applications, the transition from laboratory to manufacturing, and bridging multiple disciplines.

BASIC BIOLOGY

Improving our understanding of nanotechnology and how it can be applied to oncology rests, in part, on improving our understanding of basic biology and the pathogenesis of cancer, as well as biomarkers for cancer, some speakers noted. The dearth of good biomarker targets for prevention, diagnosis, prognosis, treatment, and monitoring is currently

a limitation on development of nanomedicine for oncology and more generally. For nanomedicines for cancer prevention, for example, there needs to be a better understanding of what a precancerous lesion is, Dr. Hawk noted, and improved sensitivity and specificity of the technologies used to detect preinvasive neoplasia or early-stage cancer. Also needed are ways to identify populations at risk for prevention studies, and to identify meaningful endpoints for cancer prevention trials. "There is great promise in measuring multiple biomarkers for early detection, but that promise remains a promise. It is not yet demonstrated, certainly, in the context of prevention," Dr. Hawk said.

Dr. Barker added that "If I look at least at where we are in regulatory science today, we're thinking about biomarkers, and how you qualify them, how you use them in trials to directly or indirectly measure what you are trying to measure. This may be one of the most powerful avenues that nanotechnology has to bring to the table in terms of what biomarkers could be, and how you might use them." The Institute of Medicine recently released a report on the challenges of biomarker evaluation (IOM, 2010).

In some cases, the biomarker knowledge needed to move the field forward is already developed, but not applied due to lack of validation and clinical adoption, Dr. Rogério Sá Gaspar, full professor in pharmaceutics at the University of Lisbon, pointed out. "Currently we have scientific knowledge and technology to genetically profile every single patient, and we know that we have 120 drugs on the market that will behave differently according to their genetic profiling, but we're not doing that. So it's not only about the technology and the regulation, it's also about healthcare and medical practice, and how we do integrate the different components of the sector," Dr. Gaspar said. Dr. Gaspar called for understanding underlying basic molecular mechanisms and integrating anatomy and physiology issues with pathological disease state and disease progression when designing nanomedicines, which Dr. Duncan echoed by asking that the disease, and not materials science, should be the driver of nanomedicine design and development. "I don't care whether it's a small molecule, a liposome, or a PEGylated liposome—the disease should drive it," she said, and Dr. Grodzinski, director of the NCI Office of Cancer Nanotechnology Research, added that "we need to listen to oncologists about where the most relevant potential need for nanotechnology exists, and how best to apply what technology has developed there." He suggested picking problems to address with nanotechnology that conventional technology currently can't solve.

Dr. Duncan added, "We really need to look at the clinical background, pathology, and the biology. People need to look outside their nano journals and into some of the founding literature of biology. . . . I'm not

knocking the materials science. But, for example, we know from the whole antibody field that antibodies and proteins have problems when we inject them into people and cause immune reactions. So decorating the surface of particles with some of those for targeting is not such a good idea. Just sitting down as a group around the table and deciding what we want to make will really run us forward in keeping it simple and working. " She later claimed that "ninety-five percent of the experts that we see are not prepared to look outside their box. The biggest challenge for all of us is harnessing this multidisciplinarity. We have to join together the fields and know what we did—what worked and what didn't work—and then we'll go forward along the road more quickly."

STRATEGIES FOR IMPROVING NANOPARTICLE TARGETING EFFECTIVENESS AND EFFICIENCY

Workshop speakers and participants discussed the need for and strategies for improving targeting capabilities of nanotherapeutics and imaging agents. One key question that needs to be addressed is whether cancer-targeting molecules are reliably attached to the nanoparticles, Dr. Curley and Dr. Li pointed out. "We are faced with tracking every component of our particles, and we can't assess every single component just by putting an imaging agent on one component," Dr. Li said. He added that one has to separate the effect of passive versus active targeting, which is difficult to do. "You see localization at your target, but how do you know it is passive targeting, and how much of it is achieved through active targeting?" Dr. Li asked. He noted that researchers at the University of California, San Francisco, showed that when they tested the liposomes they developed that were covered with antibodies for the HER2 receptor, the actual localization to the tumor was the same whether they had active targeting with the attached antibodies or just passive targeting with naked liposomes. "It is just an internalization into the cancer cell that was facilitated, so it was more pharmacodynamics that they affected with the active targeting but not pharmacokinetics," Dr. Li said.

Dr. Desai added that "If these nanoconstructs have been developed to target certain specific locations, we need to establish those tests that define the targeting and show the mechanism of action or mechanism of transport, so we can then design target-specific studies to establish efficacy." For example, to show that Abraxane was entering endothelial cells via active caveolar gp60-type transport, he put in an inhibitor to the caveolar process and showed that when that inhibitor was used, the level of Abraxane detected in tumor tissue dropped down to that of conventional non-albumin coated Taxol, which only has passive transport into tumor cells (see Figure 6).

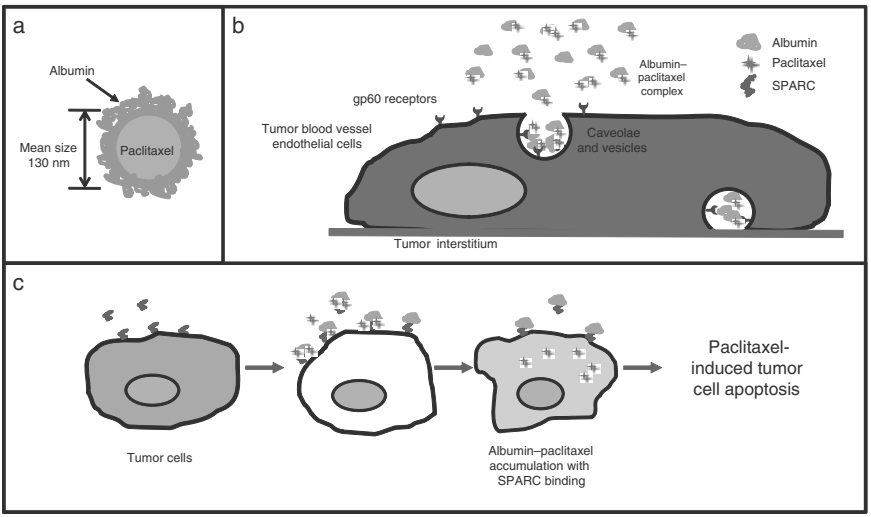


FIGURE 6 The nab technology platform: harnessing endogenous albumin pathways. (a) Particles are injected into circulation, whereupon (b) they dissociate into individual albumin-bound paclitaxel complexes at concentration below threshold. Following dissocation, active receptor-mediated transport the albumin–paclitaxel complexes across the cells via transcytosis mediated by two postulated mechanisms of action: gp60 and caveolae. (c) Active binding of albumin-drug complex by SPARC in tumor, leading to paclitaxel-induced tumor cell apoptosis.
NOTE: gp60 = endothelial cell surface receptor that mediates transcytosis; nab = nanoparticles albumin bound; SPARC = secreted protein, acidic and rich in cysteine
SOURCE: Desai presentation (July 12, 2010).

Both Dr. McNeil and Dr. Duncan pointed out that researchers and regulators have to be aware that changes in the surface of a nanomaterial, such as PEGylation[1] to avoid excretion or platination for imaging purposes, can dramatically alter biodistribution and other performance characteristics. "How we process these nanomaterials is critical. A platinated surface is very different from an empty surface and as soon as you start putting a drug in them or functionalizing them, their performance changes a lot," said Dr. Duncan. Dr. McNeil added "If you change anything on the surface, it becomes a new nanoparticle."

[1] PEGylation is when polyethylene glycol molecules of a given length or length range and given functional groups are attached to a particle in order to confer beneficial characteristics.

DESIGN COMPLEXITY OF NANOMATERIALS FOR MEDICAL APPLICATIONS

There was much discussion about how simple or complex nanomedicines should be, with some speakers cautioning against overengineering nanomedicines with combination constructs and sophisticated structures that may not be relevant or necessary. "The big problem of therapeutics is not so much targeting—it is a great thing if you can get in front of the magic door with the magic key—but to get to that point, you need to make it across so many different sequential biological barriers and the addition of targeting molecules to nanoparticles makes it so much harder to get them to the target lesion, because of the additional transport complexities that are brought in by the target moiety," Dr. Ferrari said. "Make your nanoparticles as simple as possible, but not any simpler because we have a complex problem to solve."

Others suggested limiting the complexity of nanoparticles to simplify the testing that will have to be done to show their safety and effectiveness."If we can make things as simple as possible, that will be better for the regulatory process, approval, and moving to the clinical environment," Dr. Grodzinski said. But Dr. Gaspar countered, "we cannot make simpler what is complex," which Dr. Ferrari echoed by saying that within oncology "the low-hanging fruits have been taken care of, and unless we come up with a true paradigm change, it is not going to be that simple. So don't keep it simple." Dr. Grodzinski then clarified his previous statement by saying "Limit complexity to a dominion that allows you to cure cancer."

Dr. Barker added, "I don't actually think that anything we're going to be doing in the future is going to be very simple. We're going to sort out these molecular pathways that lead to cancer, and there are going to be a finite number of them, but every individual is going to have a series of changes along those pathways that are going to be a little different. Nanotechnology will allow us to actually functionalize [nanomaterials] in multiple ways that we could never do if we were doing this in serial fashion along the paradigms we currently have. So embrace complexity, because that's what you've got to deal with." Related to the complexity versus simplicity issue, Dr. Josephson pointed out the difficulties in assessing what research will be truly clinically translatable. "How do we decide what is clinically translatable and what isn't, and when to abandon things?" he asked.

TRANSITION FROM THE LABORATORY TO MANUFACTURING

Several speakers addressed the need to improve the scale up and quality control of nanomedicines. "You have to scale up [production of]

the particle that works in the small mouse so it also works for people and meets quality control requirements," Dr. Ferrari said. He suggested that photolithography methods address both scale-up and quality control issues. (See Box 3.)

Dr. Curley voiced concern that proteins may be reliably attached to nanomaterials in the lab, but it is unclear whether the attachment methods used will scale up for production of larger quantities of the nanomaterials. Dr. Li added that quality control is more cumbersome for multicomponent nanomedicines because one has to do quality control for each component first before they are combined, and then do quality control of the combination. Dr. Zhao pointed out that many nanoparticles adsorb proteins found in the body, and this causes aggregation that changes their metabolism and their biological behavior in the body.

Dr. Desai noted that one key hurdle is being able to reproducibly manufacture complex nanomaterials, and he recommended testing them with orthogonal tests that assess the same thing but use different instrumentation, "because you can get artifacts if you just stick to one technique," he said. He stressed the importance of fully characterizing and defining nanotechnology products. But characterization of nanomedicines is just one of the first steps that must be taken to translate them into the clinic. Another major challenge is ensuring that nanomedicines are consistently and reproducibly manufactured, Dr. Desai pointed out. "We had many years of headache and heartache trying to get to that level of good consistency and reproducibility. You have to put in appropriate in-process controls and the finished product tests to define the product and to define your manufacturing process. Good engineering and manufacturing skills are essential," Dr. Desai said. Dr. Libutti added that one major concern FDA raised at his IND meeting for the nanoTNF medicine he created was that the particles should be uniform in size and substance when his lab characterized them.

Dr. Heath noted that antibodies that are frequently used as probes in nanodiagnostics, such as in barcode technology, are highly variable from batch to batch. "If you buy a new batch of antibody, it changes your entire calibration for this thing—it is an absolute killer. So even though you know you can do this, it makes it an academic exercise until you get around this antibody problem. I don't know a solution to that, other than get rid of the antibodies," he said. "The solution is finding non-biological capture agents, things where you make them once, you make them the next time, and the next time, and they are the same every single time, and you can guarantee a calibration, your training set, etc."

Dr. McNeil added that this was a major problem for many types of nanomaterials. "You have to tightly control batch-to-batch variability in your manufacturing and development process. You have to make sure

that you know which parameters influence biocompatibility for your particular nanoparticle concept and be able to control that with each subsequent batch that you manufacture," he said. He noted that some nanomaterials, such as liposomes, are well-suited for mass production and have an ease of scale up, but it may take months to years to fine-tune their formulation so their drug contents are stable and are not released too early.

Dr. Duncan stressed the importance of knowing the impurities that might be linked to nanomedicines. "We have to know what the weaknesses are so that we can make a calibration that we can validate, and we can show a regulatory agency that we know what we have in the bottle every time we make it, and that the impurities are going to be safe in that context," she said.

Dr. Duncan added that it is important to fully characterize and test each type of formulation of a nanomedicine. "We rarely give a drug to a patient on its own. So we do all of this preclinical work and then we are asked for a tablet formulation or an injection formulation that will be stable on the shelf for a year. So now we have all these other bits that the nanomedicine can interact with, and that can change its safety, efficacy and pharmacokinetics. We need to really reflect upon those things and look down the road while we're still at the beginning," she said. Dr. Hawk pointed out that most nanomedicines for prevention currently being developed must be administered intravenously, and urged more development of those that can be taken orally, on a regular, long-term basis, as that is needed for a cancer preventative. "IV administration may be acceptable in those at very high risk if done on an intermittent basis, but is not applicable to the majority of the population at risk, looking for preventive strategies." he said.

BRIDGING MULTIPLE DISCIPLINES

Several speakers echoed the sentiment that there need to be more bridges between the multiple disciplines needed to bring nanomedicine to fruition. As Dr. Ferrari pointed out, nanomedicine is highly interdisciplinary, requiring the expertise of clinicians, materials scientists, mathematicians, biologists, molecular biologists, physicists, and chemists. "In my group I have about 150 people right now, and I cannot think of two that have the same background," he said. Dr. Ferrari added that it is hard to find institutional setups that enable such multidisciplinary, team research, while at the same time enabling researchers to pursue their own individual careers. Dr. Curley added that editors were having trouble finding reviewers for his journal articles because they cover physics, chemistry, biology, and cancer, and no one is an expert in all those fields.

BOX 3

Manufacturing Nanomaterials

To make the manufacturing of nanomedicines more efficient, reliable, and less expensive, researchers are applying some of the approaches used to manufacture semiconductors to the production of nanomedicines, Dr. DeSimone, Chancellor's Eminent Professor of Chemistry at the University of North Carolina Chapel Hill and William R. Kenan Jr. Distinguished Professor of Chemical Engineering at North Carolina State University, reported. This involves mass-producing nanostructures by removing or adding material to a surface using microscopic lithography. For example, with the Particle Replication In Non-wetting Templates (PRINT) system that Dr. DeSimone developed, silicon wafer surfaces are coated with fluoropolymers and then etched with a photochemical process to create a mold for nanomaterials. To scale up and produce large quantities, he then uses a "roll to roll" process similar to what is used in the film industry. With this process, the mold, in sheet form, is matched to a delivery sheet that is used to form the actual nanomedicines, which are peeled away from the mold sheet using a harvesting film with an adhesive on it (see figure below).

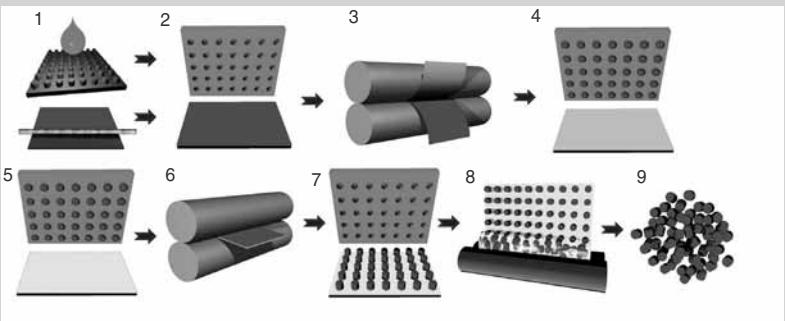


FIGURE B3-1 Diagram showing the roll-to-roll transfer templating technique. (1) The sheet shown with raised posts is the mold used to create the delivery sheet with cylindrical indentations. (2) Liquids are then spread on another sheet. (3) The sheets are sandwiched together and run through a roll-to-roll process. (4) Because of the unique surface characteristics of the flouropolymers used, the cavities are filled using capillary force without wetting the surface area between the cavities. (5) The filled cavities are brought into contact with another film that has an adhesive on it using (6) a roll-to-roll technique, and (7) the structures are transferred onto the harvesting film. (8)–(9) Structures can then be removed from the films.
NOTE: PRINT = particle replication in non-wetting templates
SOURCE: DeSimone presentation (July 12, 2010).

"One of the key things for this nanomanufacturing method is that it is a templated manufacturing process," Dr. DeSimone said. "The particles we generate are derived from the features of these master templates, so we have a way of fabricating particles of uniform size and structure." The etching process, he noted,

ensures such uniformity. “One of the key things in nanomanufacturing is reproducible manufacturing. This is where we think we have some significant advantages with a templated approach,” Dr. DeSimone said.

PRINT can be used to control the size, shape, and surface chemistry of nanoparticles, which can be made from organic materials. Many of the particles have a hydrogel as their base, to which different drugs are added, including traditional proteins and steroids as well as innovative siRNAs. Targeting moieties can also be attached with the molding process. “We can mold a wide range of chemistries,” Dr. DeSimone said, adding that the molding process enables them to form “pseudoconjugates” without the complex chemistry that is usually required to create polysaccharide–protein or other conjugated molecules.

PRINT’s molding process also has more efficiency than the standard chemical self-assembly process for encapsulating a drug in a matrix, according to Dr. DeSimone. He has been able to use PRINT to encapsulate docetaxel with PLGA (polylactic-*co*-glycolic acid) that has an encapsulation efficiency of 40 percent, he said. “In liposomes, very often you have very little latitude in controlling the amount of drugs you can put into these self-assembled structures. With our approach, we can vary the amount of drug directly within these particles, which can have a profound effect on the viability and the potency of these particles. We are getting to the point where a single particle can induce cell death, so one has to be careful [about drug concentration] now that these particles have become so potent,” he said.

Dr. DeSimone has found that particle size and shape plays a big role in how various drugs are delivered directly into the airway using a dry powder inhaler. “We can start engineering the particle size and the aerodynamic characteristics of these particles as we vary the size and shape,” he said, thereby determining whether the drug extends to the mid or deep regions of the lung or whether it mostly settles into the trachea.

Dr. DeSimone used his PRINT (Particle Replication In Non-wetting Templates) nanomanufacturing process to create a thousand doses for vaccines that are Good Manufacturing Practice (GMP)–compliant that will be tested in a phase II clinical trial. “We looked at this as [setting the stage for future] products moving forward in cancer. Our vaccine program is driving PRINT forward and allowing our other therapeutics to come in behind it,” said Dr. DeSimone. He noted for his inhalation drug program, he was able to use PRINT to make hundreds of grams of a drug in a two-day run. “We believe we can be in a kilogram quantity in an afternoon with this templated approach, and that is the direction we are going,” he said.

One aspect of his research involves modifying the deformability of the nanoparticles he engineers because there is evidence that the deformability of metastatic cancer cells enables them to metastasize (Suresh, 2007). He recently used PRINT to create extremely deformable nanoparticles, whose biodistribution he is currently testing in an animal model. “We think the ability to control size, shape, and deformation is a key component to nanomanufacturing, where calibration quality particles are intrinsically derived from a template approach using this roll-to-roll process,” he concluded.

"It is a team sport," said Dr. Grodzinski. "We have to learn a common language and work under one roof in a multidisciplinary environment." Dr. McNeil added, "It's really been a privilege working at the NCL where we've got physicists, immunologists, toxicologists, chemists, biotechnicians, and cell biologists working together. When all of us came together, we were able to offer new solutions that each of us in our own disparate fields was not able to tackle. As intimidating as it may seem at first, I would just encourage you as soon as possible, if you're a materials scientist, to have lunch with a biologist, and vice versa."

Dr. Jonathan Sackner-Bernstein, associate director for post market operations at the Food and Drug Administration's Center for Devices and Radiologic Health, pointed out that technological advances often stem from the synergy between multiple disciplines, and both Dr. Duncan and Dr. Barker pointed out that what is known in one discipline, such as polymer science, is news to another discipline. "I'd suggest that we not reinvent the wheel in terms of polymer science, but take advantage of what we know already," Dr. Barker said.

But she added, "It is still difficult in this environment, where we focus so heavily on the individual investigator that we are really making it difficult to do team science. We have got to change that." Dr. Gaspar also called for more collaborative efforts with diagnostic companies, imaging companies, and drug companies working together to develop nanoproducts for the clinic.

NCI Alliance for Nanotechnology in Cancer

Launched in 2004, the NCI Alliance for Nanotechnology in Cancer's mission is to harness the power of nanotechnology to change the way cancer is diagnosed, treated, and prevented. Through its programs and initiatives, the Alliance is committed to building a community of researchers dedicated to using nanotechnology to advance the fight against cancer.

The Alliance is focused on team science and has multiple interagency collaborations, including those with the National Institute of Standards and Technology, the Food and Drug Administration, the National Institute of Environmental Health Sciences and the Environmental Protection Agency.

A major goal for the NCI Alliance for Nanotechnology in Cancer is to quicken the pace of nanotechnology discovery and development efforts, and to lower the barriers to commercialize these advances for the benefit of cancer patients. "The Alliance is an applications-driven activity. We are not interested in just fundamental science, but about changing the lives of patients," said Dr. Anna Barker, former deputy director of the National Cancer Institute. "We built this Alliance to commercialize technology, and

we have over 50 companies, either created by or associated with the Alliance, and over 200 patents and disclosures have been filed."

The Alliance has four major programs, which are described in the following sections.

Centers of Cancer Nanotechnology Excellence (CCNEs)

The CCNE network designs and tests nanomaterials and nanodevices, and translates their use into clinical research. The CCNEs will bridge gaps in the development pipeline from materials discovery to testing in clinical trials.

By balancing structured directives with investigator-initiated research, the CCNEs bring together the interdisciplinary teams from existing NCI resources and provide the infrastructure necessary to develop and translate nanotechnology advances to the clinic.

Multidisciplinary Research Training and Team Development

The Alliance supports training and career development initiatives to establish integrated teams of cancer researchers, epidemiologists, engineers, and others to approach the fundamental challenges of cancer using cancer biology, physical science skills, and the knowledge base of nanotechnology. The NCI is initially using existing training and career development mechanisms to direct talent to this area as quickly as possible. The NCI also encourages program development with interfaces to the training programs of other federal agencies.

Nanotechnology Platforms for Cancer Research

The NCI has identified specific technology requirements and cancer biology problems that constitute critical nanotechnology platform needs for cancer. These directed research programs are funding technology development projects through both grants and contracts overseen by project specialists.

These projects are aimed at deployment for clinical application in cancer research, and applicants are required to team with the NCI to develop a dissemination plan for the technology. Examples of these platform needs include, but are not limited to

- Molecular Imaging and Early Detection,
- In Vivo Nanotechnology Imaging Systems,
- Reporters of Efficacy,
- Multifunctional Therapeutics,

- Prevention and Control, and
- Research Enablers.

Nanotechnology Characterization Laboratory (NCL)

Through a collaboration with the National Cancer Institute, the Food and Drug Administration, and the National Institute of Standards and Technology (NIST), the Nanotechnology Characterization Laboratory is developing data that will facilitate standards for nanoscale devices, and facilitate regulatory review of these products prior to market release.

Using standardized methods, the NCL characterizes the physical and chemical parameters of nanoparticles and conducts structure–activity relationships studies that aid assessments of biocompatibility. NCL also aids preclinical scale up and development, including assessing the quality, purity, and stability of nanomaterials, and conducting in vitro studies that assess sterility, cell uptake and distribution, blood contact properties and toxicity, and in vivo studies that focus on biodistribution, dose-related toxicities, and to a limited degree confirm efficacy (see Table 3).

"An investigator may have a proof of concept with a few milligrams of material, and we help them get into clinical trials over about the next year or year and a half, in some cases," said Dr. Scott McNeil, director of the NCL.

To characterize nanomaterials, NCL conducts a number of tests and assays, many of which differ from those that are commonly done to characterize small molecules (see Table 4). "We're still interested in the same physical and chemical properties assessed in small molecules, but we use a different portfolio of instrumentation to get at those," Dr. McNeil said.

The NCL's services are available to academia, industry, and government users under its application process, and its services are provided at no cost to the users. The NCL is facilitating collaborations among the NCI, academia, and the private sector to accelerate the translation of nanotechnology research into clinical advances. It also interfaces with the FDA regularly to explore issues of regulation and policy concerning nanomaterials for medical applications, and recently began collaborating with the National Center for Toxicological Research and the National Institute of Environmental Health Sciences.

"We felt that to get ahead of this field, we had to be able to characterize these materials to accelerate the translation of these agents into the clinic," said Dr. Barker. "This has turned out to be a common source of information for all the government agencies."

TABLE 3 The Nanotechnology Characterization Laboratory Conducts Physical, Chemical, and Structure–Activity Assessments of Nanomaterials

In vitro	In vivo
Sterility	Initial disposition study
Bacterial	Tissue Distribution
Viral	Clearance
Mycoplasma	Half-life
Endotoxin	Dose-range finding toxicity
Cell uptake and distribution	Blood Chemistry
Cell binding	Hemalogy
Internalization	Histopathology
Targeting	Gross pathology
Blood contact properties	Efficacy
Plasma protein binding	Therapeutic
Hemolysis	Imaging
Platelet aggregation	Transgenic and xenograft models
Coagulation	
Complement activation	
CFU-GM	
Leukocyte proliferation	
Macrophage and neutrophil function	
Cytotoxic activity of natural killer cells	
Toxicity	
Phase I/II enzyme	
Induction and suppression	
Oxidative stress	
Cytotoxicity (necrosis)	
Cytotoxicity (apoptosis)	

SOURCE: McNeil presentation (July 12, 2010).

Chinese Academy of Sciences Key Lab for Nanosafety

Recently established, China's Key Lab for Nanosafety has more than 100 researchers, students, and administrators dedicated to assessing nanoparticle properties and the hazards to humans and the environment that nanomaterials may pose. The Nanosafety Lab also makes recommendations regarding regulation of research and industrial activities on nanotechnology, fosters international nanotechnology collaborations and standards, and aids safety assessment for nanotechnology industry by developing assessment methods and procedures, and identifying toxic classes of nanomaterials.

The Nanosafety Lab engages 16 institutions and universities in China in the study of nanosafety issues, and receives its support from the Chinese government, the National Natural Science Foundation of China (NSFC) and the Chinese Academy of Sciences.

TABLE 4 Tests and Assays Used by the Nanotechnology Characterization Laboratory to Determine the Physicochemical Parameters of Nanomaterials

Small molecules	Physicochemical parameters	Nanomaterial
Elemental analysis	Composition	Microscopy (AFM, TEM,
Mass spectrometry	Physical properties	SEM)
NMR	Chemical properties	Light scattering (static,
UV-Vis	Identification	dynamic)
IR	Quality	SEC, FFF
HPLC	Purity	Electrophoresis (CE, PAGE)
GC	Stability	Zeta sizer
Polarimetry		Fluorimetry

NOTES: In many cases, different instrumentation is required to analyze nanomaterials as compared to small molecules. Nonetheless, both sets of techniques (left and right columns) are used to probe the same fundamental properties (center column). AFM = atomic force microscopy; CE = capillary electrophoresis; FFF = field flow fractionation; GC = gas chromatography; HPLC = high-performance liquid chromatography; IR = infrared spectroscopy; NMR = nuclear magnetic resonance spectroscopy; PAGE = polyacrylamide gel electrophoresis; SEC = size exclusion chromatography; SEM = scanning electron microscopy; TEM = transmission electron microscopy; UV-Vis = ultraviolet–visible spectroscopy.
SOURCE: McNeil presentation (July 13, 2010).

Center for Biological and Environmental Nanotechnology (CBEN) and International Council on Nanotechnology (ICON)

Center for Biological and Environmental Nanotechnology (CBEN)

Established in 2001, the CBEN is a federally funded National Science Foundation research center whose mission is to discover and develop nanomaterials that enable new medical and environmental technologies.

The Center's research activities explore the interface between nanomaterials and aqueous systems at multiple length scales, including interactions with solvents, biomolecules, cells, whole organisms, and the environment. These explorations form the basis for understanding the natural interactions that nanomaterials will experience outside the laboratory, and also serve as foundational knowledge for designing biomolecule–nanomaterial interactions, solving bioengineering problems with nanoscale materials, and constructing nanoscale materials useful in solving environmental engineering problems.

Though unified intellectually by the wet/dry interface, the Center's research programs are oriented toward tangible technological outcomes, or engineered systems. These are

- Nanoparticles that detect and treat disease, including those that can be used for drug delivery, photothermal cancer treatments, and imaging contrast agents; and
- Effective, high performance water purification systems that use nanoscale materials to both remove and remediate waste.

International Council on Nanotechnology (ICON)

ICON (http://icon.rice.edu) is an international, multi-stakeholder organization whose mission is to develop and communicate information regarding potential environmental and health risks of nanotechnology. ICON was founded in 2004 as an extension of the US National Science Foundation Center for Biological and Environmental Nanotechnology (CBEN) at Rice University in Houston, Texas. Composed of individuals from academia, industry, government, and non-governmental organizations from France, Japan, the Netherlands, Switzerland, Taiwan, the United Kingdom, and the United States, ICON is a technically-driven organization that does not engage in advocacy or commercial activities.

"ICON is a one-stop shop for all information related to the the environmental health and safety implications of nanomaterials," said Dr. Kristen Kulinowski, senior faculty fellow in the Department of Chemistry at Rice University and Director for External Affairs for the Center for Biological and Environmental Nanotechnology.

4

Risks Associated with Nanotechnology

Several participants noted that nanoparticles are commonly observed; these particles have both natural and human origins. "There are lots of nanoparticulates that we are exposed to every day. I am always amazed, when we think about these engineered nanoparticles as being such unusual beasts, because they are really not all that unusual," Dr. Barker said.

Nonetheless, speakers noted that nanomaterials do pose several types of potential health risks, including short-term and long-term risks to the health of those taking nanomedicines, risks to the workers making nanomedicines, and contamination risks to the environment at large. "If you are looking at the challenges to nanotechnology, I think they are going to be about safety, and the agencies of the government need to get together and work this out," Dr. Barker said.

DATA COLLECTION: BIODISTRIBUTION AND TOXICOLOGY

Dr. Ferrari and others listed several biological barriers that nanomedicines might have to surmount in order to reach their targets. These barriers include the reticuloendothelial system (RES) of the immune system, the kidneys, the liver, blood vessel walls, the tumor cell membrane, the cytosol or the nuclear membrane of a tumor cell, ionic and molecular pumps within tumor cells, and enzymatic degradation. In addition, nanomedicines might have to overcome the additional barrier posed by pressure that builds in tumors because of their leaky blood vessels, which

large molecules can penetrate. These molecules accumulate and draw in fluid, building pressure in tumor cells that impedes the entry of even small molecules, Dr. Li pointed out (see Figure 7).

The properties of nanomaterials make it difficult to predict how they will penetrate these various biological barriers or be metabolized, which in turn makes it difficult to assess their biodistribution and toxicity, several speakers noted. In most cases, one cannot predict in vivo biodistribution based on nanostructure physical and chemical properties, such as size and charge, Dr. Li noted. He added that nanostructures can distribute to various organs as intact nanoparticles or they can be metabolized or split up into different pieces, which can enter the cells of various organs and reside in them for an unknown amount of time before moving to other organs or being excreted.

"One of the most difficult parts is tracking the multiple components in vivo over time. Some may stay for a long time, some may stay for a short time. You don't even know whether they stay as one whole piece the whole time. If they stay in the liver, how long are they going to stay, and what problems are they going to cause in the future?" said Dr. Li.

Dr. McNeil added that "a huge issue that we've uncovered is stability of the particles. If a nanomaterial is unstable, obviously it will come apart, and in some cases we've seen that within a minute of introducing

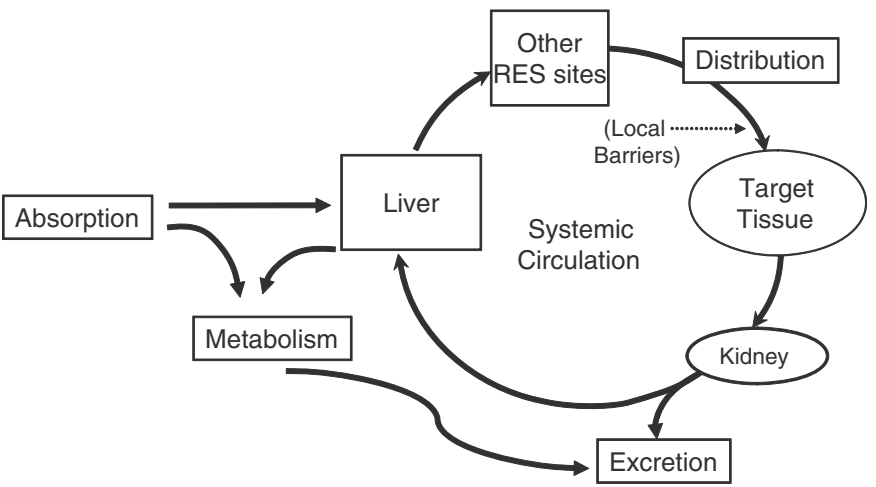


FIGURE 7 Pharmacokinetics; ADME diagram. ADME stands for absorption, distribution, metabolism, and excretion: the four biological processes that are assessed when a therapeutic or other systemic or topical drug, device, or biologic is evaluated for toxicity.
SOURCE: Li presentation (July 12, 2010).

it intravenously. Other particles are covalently bound and do not cleave, so the drug, even if it makes it to the tumor, will not come apart. It is not effective because the drug is not released and cannot interact with its target enzyme."

Dr. Ruth Duncan, professor emerita of Cardiff University and visiting professor at the University of Greenwich, stressed that the pharmacokinetics (PK) are different for nanoparticles, given that they can enter cells, and that one needs to show microscopic distribution as well as macroscopic distribution. "It's a different kind of paradigm from just using the old-fashioned cells that we were using for small molecules. The pharmacokinetics is totally different," she said. "You need quantitative PK studies on the whole body as well as at the cellular level." Dr. Li added, "macroscopic distribution doesn't imply microscopic distribution. So even if you have macroscopic imaging, it doesn't tell us enough of what is happening in vivo." Dr. Gaspar stressed assessing both pharmacokinetics and pharmacodynamics when evaluating the biological effects of nanomedicines, and having translational models adapted to the specific questions that nanomaterials raise.

In addition, Dr. DeSimone cautioned that deformability is a characteristic that needs to be measured for nanomaterials. He described that deformability is commonly measured in biology: the age of a red blood cell can be estimated from its deformability and researchers have demonstrated that metastatic cancer cells are sometimes much more deformable than their non-cancerous counterparts (Suresh, 2007). In contrast to biological materials such as red blood cells or cancer cells, deformability has not been thoroughly explored as a characteristic impacting biodistribution and toxicity of nanomaterials. He described experiments in which his lab has begun to look into nanoparticle deformability; intravital microscopy—microscopic imaging done on live subjects in vivo—has resulted in a wealth of data. Results show that deformability can reduce both formation of aggregates in the lungs and uptake in the liver. In addition, Dr. DeSimone described how tuning nanoparticle deformability could help improve intracellular uptake of nanotherapeutics.

Reflecting Dr. Li's statement that it is difficult to predict nanoparticle biodistribution and toxicity, Dr. DeSimone pointed out their experiences when testing the biological effects of PEG-based nanoparticles decorated with transferrin or antibodies to transferrin receptors (both proteins that bind transferring receptors); tranferrin receptors are overexpressed in some types of cancer. DeSimone and colleagues hypothesized that these nanoparticles could be loaded with anti-tumor drugs, the antibodies would target cells of interest, thus effecting preferential delivery of drug to tumor. However, when researchers tested the toxicity of the nanoparticles in the absence of any drug, it was found that the nanoparticles

themselves possessed the ability to induce cell death in certain types of cells (Wang et al., 2010).

Dr. Li pointed out that the route of exposure of nanomaterials will dictate, to some degree, the specific fate of them in the body. Nanomaterials applied via inhalation will have different biodistributions than those applied to the skin, taken orally, or taken intravenously. "If you inhale nanotubes versus inject them, you'll have totally different biodistribution, toxicity profiles, and so on. Those considerations do not vary as much with small molecular agents," Dr. Li said.

Further complicating biodistribution assessments is that the binding kinetics between nanomaterials and proteins are not well known, nor is it fully known how different components of nanostructures are metabolically processed and excreted. "All these special ADME [Absorption, Distribution, Metabolism, Excretion] considerations for nanomaterials that are quite distinct from those for small molecular drugs may hinder the development of nanomedicine, as this is just a partial list of the potential concerns that we have on different classes of different materials that we need to define before we get them into the clinic," Dr. Li concluded, referring to the concerns shown in Figure 8.

Some effort to fill in these knowledge gaps have been made, Dr. Zhao noted, especially in regards to toxicity assessments. Studies have documented to a limited degree such factors as the relationship of response to nanomaterial dose, degree of aggregation, size, or structure, and methods have been developed to quantify nanoparticles in vivo, he said. Dr. Zhao and his colleagues at the Chinese Academy of Sciences have published about 60 papers in nanotoxicology, as well as completed a 10-volume set of nanosafety books that was published in Chinese by a scientific press in Beijing. He noted that there also is a book on nanotoxicology that was published in English in the United States in 2007 (Zhao and Singh Nalwa, 2006).

Dr. McNeil added that characterizations of more than 200 nanomaterials at the Nanotechnology Characterization Laboratory, including 50 animal studies have revealed a few basic principles about nanomaterials and their effects in the body. These studies indicate that nanoparticles with high surface charge are cytotoxic regardless of particle type, and that uncoated nanoparticles will accumulate in the liver and spleen, and they are more likely to be digested by phagocytes, unlike those that are PEGylated.

"We found that some of our in vitro results, at least for optimization, do in fact mimic what we're seeing in vivo," Dr. McNeil said. "We can begin to predict, for example, what PEG length is best for a particular protein that's used for a targeting agent, but I can't look at a nanoparticle and tell you X amount will go to the liver and X amount to the spleen.

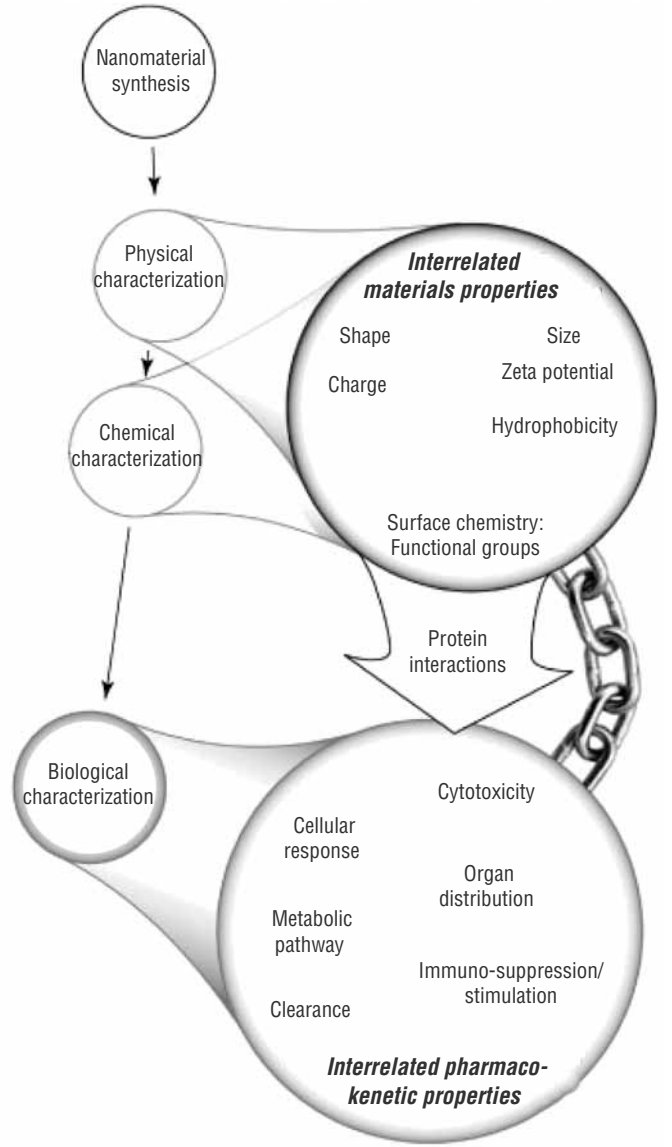


FIGURE 8 Special ADME considerations for nanomedicine.
NOTE: ADME = absorption, distribution, metabolism, excretion.
SOURCES: Li presentation (July 12, 2010) and Fischer and Chan (2007). Reprinted from *Current Opinion in Biotechnology* 18(6), H. C. Fischer and W. C. Chan, *Nanotoxicity: The growing need for in vivo study*, pp. 565–571, Copyright 2007, with permission from Elsevier.

We can't provide that level of detail. All we can do is just point out trends at this point."

Data at the National Characterization Laboratory show that surface charge, size, and hydrophobicity influence biocompatibility, he added. "We know that in our hands, every nanoparticle is unique. Just simply changing that particle—it's surface charge or the length of the PEG—makes it almost a completely different entity, even if it's still within the same class," Dr. McNeil said.

Dr. Kulinowski noted that there are more than 4,000 papers in the International Council on Nanotechnology database relevant to nanosafety and nanotoxicology of medical or environmental nanomaterials. But little of this data is what she termed "regulator-ready" data. "The majority of the papers are hazard-related rather than exposure-related, and by far the majority of those are cell culture studies. So the relevance of those papers that say 'nanoX kills 50 percent of the cells at this dose' to a person taking a drug or using a consumer product is very low. While we might be able to appreciate that there's a lot of work being done in this area, we're not getting to that next stage yet where we can say what it means for decision making," Dr. Kulinowski said.

The International Council on Nanotechnology conducted a workshop aimed at answering the question how long would it take to develop a model that would be able to predict nanomaterial behavior in biological systems and the environment. The outcome of that workshop was that it would take ten years to understand the dynamic nature of nanomaterials, Dr. Kulinowski reported. "We need to understand surface interactions much more than we do now, as well as a variety of other aspects in order to get to that goal of being able to look at the physical and chemical properties of a nanomaterial and be able to say, 'well here's how it's going to interact in a cell, in a biological fluid, in a sand bed, river, etc.'"

So despite the emerging body of knowledge on nanotxoicity, often multiple studies are needed to characterize complex nanoparticles and show where they are likely to be distributed in the body when conducting clinical trials. Some of these studies are rather esoteric, Dr. Desai pointed out. For example, one might have to do x-ray diffraction to show the amorphous or crystalline characteristics of the nanoparticle, or electron microscopy, as well as other tests specific to the construct. "These can be complex constructs, where you have not just the drug, but you maybe have polymers, different targeting agents, and many other different components. It is very important to understand how all these interact," Dr. Desai said.

Dr. Gaspar questioned the relevance of in vitro models and certain animal models when making biodistribution and toxicity assessments of nanomaterials, and stressed the need for in vivo studies.

OCCUPATIONAL SAFETY

"Occupational safety is a critical issue," said Dr. Kulinowski. "No matter what we're doing in nanotechnology, that has to be a consideration. Workers, whether they be researchers in the laboratory or production workers, are likely to be exposed to nanomaterials in higher quantities and for longer periods of time than consumers or even patients."

Dr. Kulinowski noted that although there are numerous journal articles that touch on nanotechnology occupational safety issues, few address such practical questions as safe exposure levels for nanotechnology workers. "As a result, we don't have any occupational exposure limit for nanoparticles," Dr. Kulinowski said. She suggested translating the information the pharmaceutical industry has acquired on how to safely handle fine powders with high bioreactivity to workers handling nanomaterials. She also pointed out that the International Council on Nanotechnology recently established an open-source website for sharing information about occupational practices for the safe handling of nanomaterials that they call the "GoodNanoGuide." Multiple stakeholders contribute, share, and discuss information on this site, which is modern, interactive, and up-to-date.[1] "We're looking at tasks that might be performed in a manufacturing or research environment and saying 'here are the potential human exposures, and here are the potential controls that you might want to use,'" Dr. Kulinowski explained.

She added that there have been discussions about establishing medical registries and medical surveillance programs to document health risks in those who work with nanomaterials. The National Institute of Occupational Safety and Health's most recent statement about this is that it is premature to set up a medical surveillance program or registry of workers, according to Dr. Kulinowski, but she added that the agency continues to explore this possibility. She noted that it is difficult to identify the demographics of the nanomaterials worker because nanotechnology is used in such a wide range of fields, including the chemical industry and the pharmaceutical industry. "Getting a handle on who they are and what the tasks are is very difficult," she said, let alone what types of measurements and medical tests would be made on these workers.

In his talk, Dr. Zhao stressed the need to distinguish nano-specific risks from other manufacturing risks. He gave an example of a paper which linked exposure to nanomaterials of workers to serious lung disease (Song et al., 2009). This article created a media sensation, with *Nature* publishing a news article with the headline "Nanoparticle safety in doubt," and most Chinese newspapers reporting that the nanoparticles had killed workers.

[1] See http://GoodNanoGuide.org.

But the situation was more complex than how it was initially reported. The patients with lung disease were working in a workshop used to heat plaster, and the plaster contained some titanium oxide nanoparticles that were released in the plaster fumes and found in the patients' lungs. The nanoparticles were contained within polyacrylate esters. A study in animals by Dr. Zhao and his colleagues suggested that the lung toxicity was not due to the nanoparticles, but rather due to the fumes produced by the heating of the polyacrylate esters. He called for more assessment technologies and procedures to investigate potential nanotoxicities.

NANOMEDICINE SAFETY

Dr. Curley noted that the long-term toxicities linked to nanoparticles used in medicine are not known, giving the example of carbon nanotubes. "Single-walled carbon nanotubes are fascinating from a physical–chemical point of view, but they are also incredibly rigid and stable structures, so are those going to be safe to deliver to a patient over the long term?" Dr. Curley asked. He said one study found that aerosolized carbon nanotubes were toxic when delivered to the lungs of rats—they developed something akin to the black lung disease seen in coal miners. When asked by Dr. Bahadrasain how to reassure the public that the safety of nanomedicines is not a problem, Dr. Curley responded, "We need to do the preclinical and clinical toxicology and toxicity studies that will demonstrate that to the best of our ability, there are no long term effects with the nanomaterials we are using.

Dr. Duncan noted that the safety issues linked to nanomaterials depend not only on the material, but how it is used. She pointed out that using nanomaterials in MRI imaging, in which patients are given a very low dose of the materials only once or twice, poses different risks than treating them with a nanomedicine for months or longer. "It's really important, when people ask the safety question, that we relate it to a particular material and a particular use, route of administration, and dose," Dr. Duncan stressed. Dr. Curley agreed, noting that "you may be able to use things like quantum dots in an in vitro diagnostic system that you would never give to a patient." Dr. Sackner-Bernstein added, "It doesn't mean that carbon nanotubes are not a potential application as medical devices. It just means you've got to make sure that the occupational health issues are taken care of, and that you're not using them as an inhaled device or drug."

Dr. Libutti pointed out that "there is a lot of fear in the unknown. One of the biggest challenges for us is to turn the unknown to the known so we don't have a lot of unrealistic fears." Both he and Dr. Barker noted that this fear of the unknown slowed down the application of recombi-

nant DNA technology because of the numerous restrictions on how the technology could be used initially, but eventually those restrictions were relaxed once its safety was shown. "Because of the natural fears that folks have and the predilection for watching sci-fi movies, we are going to need to go through that same evolution with nanotechnology," he said.

Based on his experience with Abraxane and five other nanomedicines, Dr. Desai said the standard battery of toxicology studies are sufficient to establish safety. "Whether you are testing a small molecule or a biologic or a nano-type construct, the tests are adequate to define the toxicology. Through the formal toxicology studies which any of you do in the standard development of drugs, those studies are pretty thorough. You look histologically at every possible organ, do all the blood chemistries, so if there is any particular toxicity, whether it be nanoparticle-related or not, you should be able to find it. I know it has been talked about that nanoproducts may have a different toxicology profile, but I think that the published papers, and maybe the little bit of hype in the lay press, has probably been more as a result of occupational exposure in the heavy industry settings … as opposed to the pharmaceutical applications," he said. But he stressed designing and conducting studies to understand the disposition of the nanomaterial in vivo. "You have to understand the biodistribution, the metabolism, the excretion, and how these components degrade over time. These are all very important for the long-term understanding of the toxicology," Dr. Desai said.

But Dr. Curley pointed out that Dr. Desai's experience is with nanomedicines that have pharmacologic or biologic agents, and may not be applicable to metallic or semiconducting nanoparticles that may be used in vivo. Dr. Desai responded, "It is not so much to do with the fact that the particles we make are albumin and conventional drug molecule versus magnetic nanoparticles or whatever, but that the way to look at toxicology typically has been to take a detailed look at all the possible tissues and other biofluids. What else could anybody suggest that you look at that may give you a better idea of some other toxicology profile that isn't caught by these kinds of studies?"

Dr. Li then pointed out that the major problem in assessing long-term toxicity of nanoparticles is that many are not metabolized and excreted, unlike most other examples of nanomedicines that have been used clinically. He noted that many inhaled particles, such as carbon nanotubes, might lodge in the lung for the long term, but that potential hazard would not be discerned in a short-term toxicity study. He said, for example, that acute toxicity assessments of asbestos would not indicate that it would cause any problems, but it does cause long-term toxicity. "I don't think the acute ADME toxicology studies that we directly deal with using small molecular drugs would screen for those long term side effects," Dr. Li

said. Dr. Zhao pointed out that his study of the metabolism of nanomaterials has revealed that many bind to proteins in the body, which impedes their excretion and metabolism. "They can stay there in the body for a long time—for nine months or longer," he said. Dr. Curley added "from an evolutionary point of view, we have not evolved mechanisms to metabolize, excrete, or otherwise modify fullerenes or solid gold nanoparticles, etc."

Dr. Desai agreed that one needs to discern if the particles do not degrade, and if they do accumulate in a particular organ, it raises different questions that require different studies, "but those aren't outside of the realm of what the FDA will ask you for anyway," he said. Dr. Josephson added that "The key thing is to make sure that the nanoparticle is gone at the end of your toxicity study. If it is still there, the interpretation is that there was no toxicity seen, but the animal didn't live long enough." Taking a lesson from history, he pointed out that gadolinium chelate contrast agents were shown to be rapidly eliminated by the kidney, and thus were touted as safe as saline by their manufacturer. But those studies neglected to look at people whose kidneys did not completely eliminate the compounds. This caused a buildup of gadolinium in their kidneys which was linked to their developing nephrogenic systemic fibrosis. Avoiding this syndrome is possible by knowing the renal status of patients prior to injecting them with the contrast. "But it has heightened the issue of elimination in nanotechnology—where do things go, how long to they stay, and can they cause toxicity years and months after they have been given."

Dr. Barker noted that the safety issues raised by nanomedicines are not any different than what has been raised by biologics, and the biggest toxicity issues have not been related to long residence times of the agent in the body, but rather how these biologics alter factors that cannot be measured. For example, leukokines have prolonged toxicity that occurs long after they are administered, she said, for complex reasons that are currently unknown.

Dr. Duncan stressed "It is up to us as innovators and members of the public to continue with the regulatory agencies to evolve the process of safety assessment of nanomedicines, depending on what we are making." But Dr. Desai and others cautioned against being overly cautious about nanomedicines. "It's important that we don't create hurdles for ourselves that make it more difficult in the long run to bring innovative technologies to the patients," he said. Dr. Libutti added "We shouldn't set the bar so high that it is difficult to cross, especially with respect to cancer therapies, as we should be so lucky if the patients live long enough to see long-term toxicities from the therapies. We shouldn't regulate ourselves out of coming up with innovative therapies, worrying about fantastic toxicities that may never come to be. Certainly for the development of nanotherapies

for benign conditions, that may be more of an issue." He pointed out that if high toxicity standards were adhered to 50 years ago, there would not be a single standard chemotherapeutic on the market now.

But Dr. Libutti added that the metrics for toxicity in preclinical trials may not measure toxicities in patients who are going to live long enough to manifest them. "It is reassuring and makes you feel comfortable if you check those boxes off for your toxicity runs, because you are more likely to get your IND through. But they don't pretend to encompass as yet unrealized toxicities that new agents may develop," he said.

Dr. Heath pointed out that "every application that I know of in nanotherapeutics that has gone into the people, the net result has been to decrease toxicity. The headline should be that we have been able to engineer away toxicity to a great extent. That is something that should be celebrated in this field. We are lowering toxicity of drugs." Illustrating the importance of lowering the toxicity of current cancer medicines, Dr. Curley gave an example of one of his patients, who was a violinist when he was diagnosed with colorectal cancer metastatic to the liver. Although he has survived eight years post treatment, he experienced such severe neurotoxicity from his chemotherapy that he is no longer able to play his instrument. "We need to look not only at the survival of our patients, but what is the quality of that survival and what are the long-term effects," Dr. Curley said. Dr. Hawk added that lowering the toxicity of cancer prevention agents is the main goal for applying nanotechnology to the cancer prevention field. "Our biggest challenge is making compounds safer, so this should be a very exciting future."

RISK–BENEFIT ASSESSMENTS

Dr. Gaspar suggested that when it comes to nanomedicines, risk–benefit management is the approach that needs to be taken rather than risk assessment. "Every medicinal product has a risk. If we start to make decisions based only on risk assessment, we'll end up withdrawing the pipeline of medicinal products as a whole, and not only the nanomedicines in particular," he said. Dr. Kulinowski added that there is some social science research that indicates that consumers are willing to take greater risks for greater benefits. "It's not just about risk, it's about risk–benefit. When the benefit is low, there's a lower tolerance for risk," she said. Dr. Hawk added that risk–benefit assessments will especially underlie the usefulness of cancer preventives in a healthy population.

Dr. Sackner-Bernstein noted that FDA takes a risk-based approach when assessing the safety of medicines and devices, with more scrutiny given to those products likely to pose the most risk, but that the agency also considers risk–benefit assessments of those products, including the

potential impact on the public and whether there are alternatives that exist already to the product being considered. "We try to make sure that when there's a product that actually has impact, the barriers that it faces are commensurate with the potential impact," he said.

Dr. Duncan stressed engaging the public in risk–benefit assessments of nanotechnologies. "The public decides whether the risk–benefit is acceptable. As scientists and regulators, we have a duty to our patients to tell them accurately what the risks and benefits of the technology are," she said. Dr. Li agreed that it is important to engage the public in these assessments, but he expressed concern about the public's ability to make the scientific distinctions needed to adequately assess the risks and benefits of nanomedicines. He suggested educating the public about what nanotoxicology means in the environment or in their food versus what it means in medicine. He said that public understanding of risk–benefit is important in order for regulatory agencies to effectively communicate their work.

5

Standards and Regulation

Referencing a Congressional Research Service paper (Schierow, 2008), Dr. Kulinowski pointed out that there are numerous challenges involved in regulating nanotechnology because of a diversity of nanomaterials and their applications, a lack of characterization data, and a lack of standardization in nomenclature, metrics, and materials, and possibly inadequate statutory authority. In addition, the multidisciplinary nature of nanotechnology endeavors makes them difficult to communicate, the information needed to adequately regulate nanotechnologies may be proprietary, and there are limited resources devoted to the task.

NANOMATERIAL DEFINITIONS

Defining nanomaterials for regulatory purposes is a significant hurdle that has yet to be overcome. Dr. Duncan noted that some groups have defined the upper limit of nanomaterials as being those that measure 1000 nanometers, which covers many nano-size products already on the market. In contrast, the NNI and the FDA define that upper limit as being 100 nm. The NCL has a cutoff of 220 nanometers based on the fact that biological filters in the body are that size. Some of the fenestrations in the liver and spleen are about 250 nanometers in size, according to Dr. McNeil.

"We know we have some issues here with the terminology, and making the way we speak connect to something that a regulator or decision-maker in a company would be able to act on," Dr. Kulinowski said.

How nanomaterials are defined profoundly affect how they are regulated, she pointed out. For an example, Dr. Kulinowski showed how the EPA evolved in its regulation of nanomaterials. Initially the agency claimed that nanomaterials were not considered new chemicals, with more of an emphasis on the molecular identity of the material and not its size, shape, or surface. The agency regulated nanomaterials as falling under the domain of the Toxic Substances Control Act, and engaged in a voluntary data gathering approach initially. But now the EPA is starting to define nanoscale materials as new uses of existing chemicals, she said, which allows the agency to impose some additional reporting requirements, toxicology testing, and specific mandates for worker protection, as well as mandatory data collection.

"The EPA is shifting their emphasis from a very specific chemical definition of how the atoms are connected, to how does it act, what does it do, is it biologically or environmentally different, and does it have different physical and chemical properties that could matter in an environmental or biological system," Dr. Kulinowski said.

Several speakers called for more standards in terminology and metrics. Dr. Desai noted the importance of having an appropriate descriptive term in the label or package insert of a nanomedicine so that the clinician and patients fully understand what they are using and can make an informed decision. But Abraxane's particle size is 130 nanometers (nm) so the FDA did not allow his company to call Abraxane a nanoparticle because it was bigger than their 100 nm cutoff for nanoproducts. He added that other regulatory agencies internationally accepted Abraxane being labeled as a nanoparticle.

Dr. Sackner-Bernstein implied there might be flexibility in the FDA definition of nanotechnology. "It's about size and properties, but basically if you think it's going to behave differently, come talk to us. The last thing anybody wants is for a product to get far along and then to discover a problem. Discussing this up front, even if you're not sure, is a way to address this issue," he said. Quoting from an FDA document (FDA, 2009). Dr. Duncan added "It is quite likely that new therapeutic benefits are being derived from products that are smaller than their traditional form, but fall above the 100 nm size-range limit of nanotechnology…. Particle size is not the issue. As new toxicological risks that derive from the new materials and/or new conformations of existing materials are identified, new tests will be required."

Dr. Duncan stressed the importance of accurate categorization of materials and products. "What if we suddenly decided today that every transport system is called a plane. If we try and control a boat or a bicycle or a train using the same regulation we use for a plane it is not helpful." Dr. Gaspar agreed, "This is not irrelevant, because the problem is that

if we start calling different things the same name it will be a complete mess," he said.

NANOTECHNOLOGY STANDARDS

Some progress in developing nanotechnology standards has been made. Dr. Zhao and his colleagues at the CAS have published 21 standards for nanoscience and nanotechnology in China, three of which were adopted by the International Standards Organization. Dr. McNeil noted that standards development is one of the goals of the Nanotechnology Characterization Laboratory and that it has collaborated with the ISO and the ASTM to finalize three formal voluntary consensus standards for biocompatibility testing of nanomaterials intended for medical applications. In collaboration with NIST, NCL also developed three gold nanoparticle reference materials so results can be compared between laboratories.

The ISO has been creating standards and definitions for different nanotechnologies, according to Dr. Duncan, but these will not be broadly applicable to all the areas for which definitions and standards are needed. She stressed the need to limit definitions for nanotechnologies to the sectors in which they will be used. "If we have a particular class of materials or consumer products that needs a specific definition for regulation, they should come up with it in that sector and not try and impose it on all the other sectors," she said.

But Dr. Desai noted there is still a lack of standards for what types of tests are needed for nanomedicines. "There is no standard or general list of tests, so you have to put these tests that together build understanding of the product, and then convince the regulatory agencies that these are the tests that are needed," he said. Dr. Libutti said that during his discussions with the FDA about his clinical trial of nanoparticles of TNF, the agency made it clear that they wanted to know the fate of the particles, how the particles would be tracked, and any additional toxicities that might occur based on the fact that they are a nanoparticle. Consequently Dr. Libutti built into the trial the ability to monitor for the presence of the particles in the urine, serum, and various tissues. One of the important components of this trial, Dr. Libutti said was the ability to perform tissue biopsies in real time after the patients received the experimental nanoparticles. Using these biopsies, the investigators could assess whether the nanoparticles hit their targets.

One participant at the workshop noted that it is ironic that one has to define the trafficking of nanoparticles, when there is no such requirement for any of the small molecules that are administered clinically. "If you give systemic chemotherapy, you don't have to demonstrate that it traffics anywhere. You do a randomized controlled trial and you see what happens

with survival basically. Are we creating a new more robust paradigm that will only be applied to nanotechnology?" the participant said.

Dr. Libutti responded by noting the bar for nanomedicines does seem to be set differently or higher than for conventional small molecules, but he added "maybe that is not such a bad thing, because I think we are learning a lot doing that. I certainly wish more of that were done for the so-called targeted molecular therapies, because for many of them, we don't even know that that they are actually hitting their target."

Dr. Josephson noted that for nanomedicines that are injected, the regulatory framework is well established "because there's a long history that precedes the word nano. If there's a problem, it comes up in promoting nano as new, when it's not new as far as injectable parenterals go, nor is the history of how to handle these materials," he said.

WORKING WITH THE FDA

Dr. Desai stressed that "You need to work with the FDA and any other regulatory agency to enable understanding of the technology, whether it is from the point of view of physical–chemical characterization or from the point of view of manufacturing, because the FDA is not necessarily the experts. It is your job to explain and educate the FDA as to the particularities of your product."

He noted that most nanomedicines will likely require nonstandard type equipment for their manufacturing, with which the FDA will be unfamiliar. "Our experience with the FDA was very positive as they were keen to learn," Dr. Desai said. "They came over to our manufacturing site for an education in nanotechnology manufacturing."

Dr. McNeil concurred the FDA's willingness to be open to new information, citing how he has shown them the difficulty of addressing some of the questions they were asking of nanotechnology product sponsors. After almost three years of collaborative research with NIST that was unable to fully answer one of those questions, he approached the reviewers at the FDA and told them that the question is difficult to address, but that they were finding that it was not germane to biocompatibility. "As soon as that information was known, they realized that it may not be all that important for that specific application. My interactions with the FDA have been very positive," Dr. McNeil said.

Dr. Sackner-Bernstein noted that the FDA recently formed a council to focus on how to facilitate medical device innovation, which might include some nanotechnologies. "This council is going to focus on understanding the barriers to product development, and make sure those barriers are aligned with the clinical need. We're not going to make it easy, but we're going to make it appropriate, and that kind of appropriateness and pre-

dictability is what's going to help innovators drive forward new devices to treat these needs," Dr. Sackner-Bernstein said.

He also pointed out that FDA is working to have more integration of scientific expertise outside the agency, and that the FDA's internal scientists are working with NIST to learn more about the scientific and technical aspects of nanomaterials. But he pointed out that the FDA is always going to be behind the scientific knowledge curve. "One of the criticisms is that the agency doesn't have enough scientists to understand new science. Well, that's never going to happen, because if it's new, there's going to be only 5 or 10 people in the world who are there because they want to break the new science and develop the new products, not because they want to work at the FDA," he said. Dr. Grodzinski added, "We, in both government funding and regulatory agencies, are trying as hard as we can, so don't get too disappointed with us."

Dr. Kulinoski suggested incentives to produce and communicate risk data in a "regulator-ready" form so it not only reaches the government officials who need to consume the information, but it is written such that they can understand it and can incorporate it into their decision making.

Combination Products

What makes regulation of nanomedicines particularly challenging is that they often cross FDA regulatory boundaries by combining multiple therapeutics, therapeutics with diagnostics, or other devices with therapeutics. Dr. Desai noted that the multiple components of many nanotherapeutics may require consultation with more than one center at the FDA. For example, because Abraxane is comprised of both the biologic albumin and the small-molecule drug paclitaxel, it was regulated under FDA's drugs division, but there was a consult with the biologics division because of the albumin.

Dr. Duncan quoted from an FDA website (FDA, 2009), "FDA expects many nanotechnology products that we regulate to span the regulatory boundaries between pharmaceuticals, medical devices and biological. These will be regulated as 'combination products' for which the regulatory pathway has been established by statute." Dr. Gaspar applauded FDA's combination product regulation pathway, but in regards to diagnostics that can predict who will respond to specific therapeutics and should therefore undergo regulatory review simultaneously with the therapeutic, Dr. Gaspar added, "On both sides of the Atlantic we haven't found a common regulatory path that can look at this in an integrated form."

Generics and Follow-On Products

A major regulatory gap that needs to be addressed is how to regulate generic versions of nanomedicines, and what Dr. Gaspar termed "follow-on products" that are related to old products that were previously not classified as nanoparticles, but are considered nanoparticles today. "We are facing these problems as we speak now—they are already on the table as the generics are already here," Dr. Gaspar said. For example, Doxil is a liposome encapsulated chemotherapeutic that is also PEGylated. "When we look at potential generic formulations of this, the differences on the surface properties related to the manufacturing process are theoretically so wide that we currently cannot conceive of having a generic formulation going through as a generic product," he said. "We don't have the possibility, based only on physical–chemical data, to translate equivalence between the innovative product and its generic version."

Dr. Gaspar noted that the classical regulatory approach for a generic product formulated as an intravenous aqueous solution, such as iron oxide colloids for iron replacement therapy, does not require pharmacokinetic assessments, even if the formulation contains nanoparticles. He also pointed out that not only can the surface characteristics of a generic nanomedicine differ from its original formulation, but that the manufacturing process can be completely different. The so-called generic formulations of iron-oxide nanoparticles behave differently in animal and clinical studies, he said.

Dr. Desai concurred that generic nanomedicines pose potential regulatory problems. "The generics ultimately will have to show that they are equivalent to the nanotechnology product in question, so what tests would they use to show this?" he asked, and stressed that it is important to fully characterize nanomaterials, not only so they pass regulatory muster today, but so there is a basis in which to compare generic versions that are created later.

SETTING REGULATORY POLICY

There was much discussion at the workshop of how much regulation is enough regulation, with some participants advocating for closing current regulation gaps, but not overregulating nanotechnologies such that innovation is stifled. Dr. Duncan noted that overregulation of clinical research in the United Kingdom has reduced productivity without enhancing safety via excessive bureaucratic requirements and procedures. This resulted in the pharmaceutical industry now recruiting only one-third the number of patients to clinical trials in the UK compared with the period before the UK revamped its clinical research oversight so as to harmonize with European directives.

"I hope the standards and terminology that we're using and putting into the regulatory setting will be appropriate to make things a safe and as low-risk as possible, but will not take us back to a position that's stopping these sorts of technologies going forward," Dr. Duncan said. Dr. Barker agreed saying "I hope we don't overregulate this field to a point that we can't do anything."

Dr. Gaspar stressed that a new regulatory framework for nanomedicines is not necessary. He noted that current regulation of nanotechnologies continues to change as the science is updated. "So we don't need a legally binding, completely different regulatory system in order to integrate science," he said. But Dr. Gaspar added "We need to be very careful with the gaps between existing regulations, because those gaps are the traps where once we have an accident that is labeled nanotechnology in medicine, it will impact all of the overall products across the board in different technologies." Dr. Zhao concurred with the need to be proactive in the risk evaluation of nanotechnologies so accidents do not occur that turn the public against the field. He suggested verifying the suitability of regulations already in place for nanoproducts, and creating new laws and regulations to cover any regulation gaps that might lead to nanotoxicities.

Both Dr. Gaspar and Dr. Duncan called for regulating medical nanotechnology products versus regulating nanotechnology. "Nanomedicine is not focused on the processes of nanomedicine technology, but is focused on the patients. And that completely changes the environment in which we are discussing the science and the regulation," Dr. Gaspar said.

Dr. Kulinowski noted recent attempts various states have made to close regulatory gaps they see in nanotechnology oversight. A recent report by the Wilson Center (Keiner, 2008) looked at the potential for state and local governments to take action in the absence of strong federal action. This report found that in many cases, states have been given the authority to go even beyond what the federal government imposes. "States can begin to fill in the gaps where federal law is silent," she said, "And we're beginning to see that in the State of California."

The State of California has exercised its authority under a recent new law called the Health and Safety Code, which allows it to require manufacturers to produce information. Using this law, the state required all carbon nanotube manufacturers or importers to provide analytical test methods, transport information and other relevant health and safety data by January 2010. They were given a year to respond. "They've taken a very cooperative and deliberative model for engagement with industry. They've had lots of public seminars, invited stakeholder testimony and input, and been extremely collaborative. It's really something to watch," Dr. Kulinowski said. The State of California plans to impose

similar requirements on the manufacturers and importers of other nanomaterials, such as nanoscale metal particles.

Dr. Kulinowski added that this illustrates that nanotechnology regulation can occur in a number of different ways from soft standards put out by scientific societies to more formal regulations by various state and federal agencies, including FDA, EPA, and OSHA.

COLLABORATION WITH AND BETWEEN REGULATORY AGENCIES

Several of the speakers spoke of the need for collaboration in the oversight and regulation of nanotechnology and nanomedicines. Dr. Sackner-Bernstein noted a recent fruitful collaboration between DARPA and the FDA in the development of blood farming using stem cells, which he said could serve as a model for collaboration between government agencies. At the time there was no regulatory pathway for the type of product DARPA was trying to create, so the agency collaborated with the FDA early on in the development of their blood farming program. FDA helped them determine the testing that needed to be done on their product so that eventually it would make it to the market. In a similar manner, a researcher funded through NIH who is trying to develop a nanoscale device could ask the NIH project officer to meet with the FDA and determine the information the agency will require of the device in order for it to be commercialized. "That would be something we certainly would be willing to explore, just as we did with DARPA," Dr. Sackner-Bernstein said.

Dr. Gaspar suggested looking at ways to integrate academia, industry, and regulators during the entire product life cycle, including pre- and post-market phases. "I think that is the way to move forward," he said. He recently committed to being the coordinator of the EUFETS (a European contract manufacturer for cell and gene therapy) Regulation and Science Committee, which is integrating European regulatory organization and scientific societies. Dr. Sackner-Bernstein concurred that the FDA favors taking a life-cycle approach to regulating medical products.

Dr. Gaspar, Dr. Duncan, and Dr. Zhao also called for global cooperation for nanosafety and regulation of nanotechnologies. Dr. Gaspar suggested the European Medicines Agency (EMEA) the FDA, the European Committee for Standardization (CEN), the International Organization for Standardization (ISO), the Organisation of Economic Co-operation and Development (OECD), and especially with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) work together to forge consistent regulations and standards in nanomedicine.

Dr. Gaspar pointed out that the Predictive Safety Testing Consortium

is a good example of global collaboration to improve the efficiency of procedures. He suggested establishing institutional mechanisms for global cooperation based on specific goals and a specific timeline. "We need to act globally as soon as possible on the research and development phase," he said. Despite differing national infrastructures, "We have a lot to gain in terms of communication across the Atlantic," Dr. Gaspar said. Dr. Duncan added, "Every region wants to have its nanotechnology institute and do everything. But we should have the best in the world get together and solve the [regulation] problem."

Aiding that global cooperation was the first International Workshop on Nanomedicines, which was planned for September of 2010, and was sponsored by the European Medicines Agency. A report from that workshop will identify issues and emerging science aspects, which may assist future developments in the field and be relevant to future regulatory considerations. Dr. Zhao noted the first Global Congress on Nanoengineering for Medicine and Biology, which was held in Houston in February 2010. He also said the first US–China symposium on Cancer Nanotechnology and Nanomedicine was held in Beijing in October 2008, and an international meeting on nanostandardization of biotechnology that was held in Shanghai in 2009 and had representatives from 26 countries.

6

Nanotechnology and the Public

Several speakers spoke of the need to educate the public and policy makers about nanotechnology's actual risks and benefits. Dr. Hawk said acquiring public acceptance of nanotechnologies is one of the more pressing challenges to their translation into the clinic. He cited a survey of a Swiss population in which a variety of different unknowns were raised by consumers about foods or food packaging altered by nanotechnology (Siegrist et al., 2007). The questions these consumers raised included do nanoparticles migrate?, what are the downstream environmental impacts of nanoproducts?, and do we properly evaluate their safety?

"The overarching issue of social trust comes into play with acceptance both of the technology as well as appropriate regulatory oversight in the view of the public. Questions around safety play prominently in the minds of the public," Dr. Hawk said.

Dr. Zhao noted that scientists know more about nanotoxicology than is conveyed to the public and policymakers, and even to people in the nanotechnology community. Many remain unaware of the progress being made in nanotoxicology and instead are likely to believe magnified risks of nanotechnology conveyed to them, he said. "We need to communicate with the public with respect to the safety and ethical concerns. The public is deeply concerned about the directions our society is moving in, and the technologies that are developed," Dr. Zhao said.

He noted insufficient regulatory oversight of nanotechnologies will reinforce the fears that the public has about the safety of nanoproducts. "If you do not know it, you fear it," he said, and suggested more

dialogue with the public to increase awareness and understanding of nanotechnologies, as well as more stringent regulation and oversight of these technologies. Dr. Kulinowski noted that the cosmetic products that FDA does not have premarket approval over are generating much more controversy because there's a perception that "there's no one minding the store." Several nongovernmental organizations have written reports and filed petitions for FDA to take a stronger approach toward these products, she said. "I would argue that concerns over drugs and medical devices are less because there's a perception that FDA has different, more rigorous process for screening these drugs," Dr. Kulinowski said.

Dr. Gaspar stressed that it is not just the general public that needs to be educated about nanotechnologies, but also policymakers. "Before you have a problem with the general public, you have a problem with people that are making uninformed decisions," he said.

7

Additional Challenges

A few additional challenges were mentioned by workshop participants but not dwelled on to a large extent. In addition to medicine-based approaches, a major effort in applying nanotechnology to cancer prevention is to use nanomaterials in food packaging to improve food storage so cancer-preventing nutrients in food stay fresher, according to Dr. Hawk. Cookware may also be coated with a "nanoglaze" to prevent toxic by-products of cooking from surfacing onto foods. Industry is also pursuing the development of nano-based food supplements, Dr. Hawk said. As mentioned earlier, others mentioned the need to explain the difference between risks related to nanomaterials in food or in the environment as compared to nanomedicine.

Dr. Barker noted the need for patient privacy protections with personalized nanomedicines, and the major challenge of having clinicians adopt nanotechnologies, once they are on the market. "The biggest barrier we have is convincing our colleagues to use these new interventions, to displace what they know how to do with something that they don't quite understand," she said. Reluctance to adopt nanomedicine has delayed its clinical testing, she added, noting the significant challenge of finding clinicians willing to run clinical trials of nanomedicines.

Dr. Li noted the challenge of acquiring sufficient financial funding to develop nanotechnologies and bring them into the clinic. He started a small company to fund the development of a nanomedicine, and although he raised 17 million dollars from private investors that kept him in business for two and half years, once the "dotcom bubble burst," he said it

was difficult to sustain funding. But according to Dr. Barker, nanotechnology is an area of huge investment internationally, especially by venture capital firms. "It is very exciting to all of us to see this level of interest in terms of the financing world, which will make things happen," she said. In regards to developing nanomedicines that can prevent cancer, Dr. Hawk claimed that there are major concerns by industry that such a venture will not be profitable because of the long time frames needed to conduct the relevant clinical studies, and because they may not be able to patent their discoveries.

8

Concluding Remarks

After a day and a half of lively presentations and discussions, it was apparent that nanotechnology was a promising set of technologies that had already penetrated the cancer arena, and was likely to make a much bigger impact in the field in the future. There was an acknowledgement by many that much more needs to be understood about nanotechnologies to commercialize them and ensure their safety and effectiveness. Additional challenges may impede progress in bringing nanotechnologies into the clinic, including public wariness of such innovative materials, a lack of nanotechnology manufacturing and testing standards, and gaps in regulation.

But because of the unique properties of nanomaterials that make them more likely to concentrate in tumors, penetrate various biological barriers that conventional small molecules cannot cross, and safely encapsulate toxic medicines and carry large payloads, the most common opinion seemed to be that nanotechnology would improve oncology. Jim Heath echoed this sentiment when he said, "I think it is worth noting that every application that I know of in nanotherapeutics that has gone into people, the net result has been to decrease toxicity. We talk about all these [challenges], but the headline should be that we have been able to engineer away toxicity to a great extent. That is something that should be celebrated in this field."

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Acronyms

α-CD20	anti-CD20, CD20 is cluster of differentiation 20, a cell surface protein
α-CD33	anti-CD33, CD33 is cluster of differentiation 33
ADME	absorption, distribution, metabolism, excretion
Apo-A1	apolipoprotein A1
ASTM	organization formerly known as the American Society for Testing and Materials
βhCG	β subunit of human chorionic gonadotropin
BNP	brain natriuretic peptide
CAS	Chinese Academy of Sciences
CBEN	Center for Biological and Environmental Nanotechnology
CCNE	Center of Cancer Nanotechnology Excellence
CEN	European Committee for Standardization
CFU-GM	colony-forming unit granulocyte macrophage
CK-MB	creatine kinase MB fraction (the MB fraction is most specific to cardiac muscle)
CLIO-Cy5.5	cross-linked iron oxide Cy5.5 (Cy5.5 is a type of cyanine fluorescent dye)
DARPA	Defense Advanced Research Projects Agency
DEAL	DNA-encoded antibody barcode

DFMO	difluoromethylornithine
DNA	deoxyribonucleic acid
DOX-OXD	dextran conjugated doxorubicin
Doxorubicin-cBR96 (α-CD174)	doxorubicin conjugated to chimeric monoclonal antibody cBR96 (anti-CD174, CD174 is cluster of differentiation 174, a cell surface protein)
DTA-IL2 fusion protein (α-CD25)	fusion protein of diphtheria toxin fragment A and interleukin 2 (this fusion protein targets CD25, a cell surface protein)
EGCG	epigallocatechin-3-gallate
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
EPA	Environmental Protection Agency
EUFETS	a European contract manufacturer for cell and gene therapy
FDA	Food and Drug Administration
Genexol-PM	Genexol–polymeric micelle
GFP	green fluorescent protein
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	good manufacturing practices
gp60	60 kDa glycoprotein, an albumin binding protein
hCG	human chorionic gonadotrophin
HER2	human epidermal growth factor receptor 2
Hg	mercury
IBBC	integrated blood barcode chip
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICON	International Council on Nanotechnology
IFN-γ	interferon-γ
IL-1α	interleukin-1α
IL-1β	interleukin-1β
IL-2	interleukin-2

IL-6	interleukin-6
IL-10	interleukin-10
IL-12	interleukin-12
IND	Investigational New Drug Application
IOM	Institute of Medicine
ISO	International Organization for Standardization
IV	intravenous
KS	Kaposi sarcoma
LD50	median lethal dose
LE-SN38	liposome-encapsulated 7-Ethyl-10-hydroxy-camptothecin
LErafAON	liposome encapsulated c-raf antisense oligonucleotide
LMWP	low molecular weight peptide
MALDI TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MCP-1	monocyte chemotactic protein-1
MFNP	magneto/fluorescent nanoparticles
MIT	Massachusetts Institute of Technology
MR	magnetic resonance
MRI	magnetic resonance imaging
MTX-HSA	human serum albumin–bound methotrexate
nab	nanoparticle albumin-bound
NCI	National Cancer Institute
NCL	Nanotechnology Characterization Laboratory
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NK911	polymeric micelle carrier system for doxorubicin
NMR	nuclear magnetic resonance
NNI	National Nanotechnology Initiative
NSAIDs	non-steroidal anti-inflammatory drugs
NSFC	National Natural Science Foundation of China
OECD	Organisation for Economic Co-operation and Development
Onco-TCS	Onco-transmembrane carrier system, the drug vincristine

OSHA	Occupational Health and Safety Administration
OSI-211	liposomal lurtotecan drug manufactured by OSI Pharmaceuticals
P13K	phosphatidylinositol 3-kinase
PEG	polyethylene glycol
PEG-IFNα2a/-IFNα2b	pegylated interferon α-2a/interferon α-2b
PEG-L-asparaginase	polyethylene glycol conjugated asparaginase
PGA-paclitaxel	polyglutamic acid conjugated paclitaxel
PHPMA-doxorubicin	poly(2-hydroxypropyl methacrylate) conjugated doxorubicin
PK	pharmacokinetics
PK1	N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin
PK2	N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer backbone and pendant doxorubicin (DOX) linked via a Gly-Phe-Leu-Gly peptide spacer
PLD-E1A	pegylated liposomal doxorubicin–linked E1A (an adenoviral oncogene) plasmid DNA
PLGA	polylactic-*co*-glycolic acid
PRINT	particle replication in non-wetting templates
PSA	prostate specific antigen
RBC	red blood cell
RES	reticuloendothelial system
RNA	ribonucleic acid
RNAi	RNA interference
SGN-15	cBR96-doxorubicin immunoconjugate, SGN stands for Seattle Genetics Inc.
siRNA	short interfering RNA or silencing RNA
SPARC	secreted protein, acidic and rich in cysteine
SPI-77	sterically stabilised liposomal cisplatin
TGF-β	transforming growth factor β
TNF	tumor necrosis factor
TNF-γ	tumor necrosis factor γ
UK	United Kingdom
WBC	white blood cell

Glossary

ADME—stands for "absorption, distribution, metabolism, excretion." Mnemonic for toxicology studies needed for determining safety of a drug, biologic, or medical device intended for use in the body.

albumin—the primary protein in blood plasma.

bio-barcode—method developed to improve limits of detection for protein concentrations in samples. By coupling the protein binding events with DNA "barcodes"—unique sequences of DNA matched with specific protein targets (sequences can be random and do not need to be related to the protein)—additional sensitivity is gained because the DNA barcodes can be amplified to detectable levels using polymerase chain reaction.

biocompatibility—the degree to which a material or device can perform its function without causing undesirable immune response from the host organism or other adverse effects.

biodistribution—the locations to which materials or devices travel after placement in a living body.

biomarker—"a characteristic that is objectively measured and evaluated as an indicator of normal biological prcesses, pathogenic processes, or pharmacologic responses to a[n] … intervention" (Biomarkers Definitions Working Group, 2001). Example: cholesterol level.

biomolecule—molecule produced by a living organism, such as a protein, nucleic acid, or other biochemical.

cantilever—an object projecting out into open space with support only on one side. A diving board is an example. In microtechnology or nanotechnology, thin cantilevers composed of various materials can be used for precise measurements, such as in atomic force microscopy and the small mass measuring device discussed in this workshop summary.

cellular pumps—membrane protein complexes that transport molecules such as lipids and other biomolecules, drugs, and other chemicals into or out of a cell. Cellular pumps are involved in removing foreign substances from cells, and so adaptations to a particular drug or class or drugs can lead to drug resistance.

chemiluminescence—occurs when the energy released from a chemical reaction is in the form of light rather than heat.

colorimetric assay—a test used to detect levels of a chemical or biomolecule or completion of a chemical or biological reaction using a change in color due to change in pH of an indicator chemical, chemical composition of the reaction solution, or aggregation of colloidal particles.

contrast material—substance used during biological imaging to enhance the viewer's ability to distinguish between features. Contrast materials consist of fluorescent or radioactive molecules or atoms as well as metallic or fluorescent nanoparticles. Contrast materials preferentially travel to locations in biological samples based on their chemical and biological properties.

cytotoxic—the property of being harmful to the health of cells.

dendrimer—a branched polymer whose branching is symmetric. One or more polymers can be used to synthesize a dendrimer, and each component will affect the properties of the dendrimers. Dendrimers have discrete molecular weights and can have sizes in the nanometer range.

dose-related toxicities—harmful effects of substances related to the amount of the substance to which an organism is exposed.

ELISA (enzyme-linked immunosorbent assay)—a test which detects proteins in solutions by first selectively capturing the proteins out of solution onto a surface and then attaching fluorescent probes to the proteins. ELISA assays often probe many proteins at once using different capture agents in different wells of a microtiter plate.

endocytosis—process by which cells internalize objects and molecules.

epidermal growth factor receptor (EGFR)—a receptor that is overproduced in several solid tumors, including breast and lung cancers. Its overproduction is linked to a poorer prognosis because it enables cell proliferation, migration, and the development of blood vessels. Several FDA-approved drugs specifically target EGFR.

hemolysis—rupturing of red blood cells. The ability of a substance to cause hemolysis can be evaluated as part of a toxicological assessment of the substance.

histopathology—examination of tissue samples in order to understand disease processes in the organism from which the sample was obtained.

kinetics—in physics, the study of motion. In chemistry, the study of reaction dynamics.

leukocyte—white blood cells, which are important components of the immune system.

liposomes—small particles constructed from lipid bilayers. A liposome can carry molecules in its interior cavity; the carried molecules are most often water soluble.

LMWP (low-molecular-weight peptide)—In the context of this summary, LMWPs are components of blood samples that can potentially be used to develop new medical therapies.

MALDI TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry)—a type of spectrometry used to identify components of materials that are difficult to measure by more traditional mass spectrometry methods.

magnetic resonance imaging—in this method of imaging, a magnetic field is used to align the magnetic moments of protons in some atoms, such as the hydrogen atoms in water found in body tissues. The decay of the alignment is then measured and used to create images. Differences in contrast are due to differences in chemical properties of tissues. For example, fat has less water than blood, and so they would appear with different intensities on an image.

magneto–fluorescent nanoparticles (MFNP)—nanoparticles with both magnetic and fluorescent properties. Such nanparticles can be made from silica infused with both a fluorescent dye and iron oxide nanoparticles.

micelle—small particle constructed from lipid layers. A liposome can carry molecules in its interior cavity; these molecules are usually hydrophobic.

molecular signature—a distinctive set of biomolecules or biochemicals present in the bloodstream or a particular tissue indicating a healthy or disease state.

nanobiochip sensor—test consisting of a nano-sized capture well on a polymer base. In a single well, cells are captured, labeled, and imaged, speeding and miniaturizing multiple laboratory processes.

nanodevice—a device (medical device in this context) possessing size in the nanometer range or some property dependent on the nanoscale size of a device component.

nanodiagnostics—a diagnostic test possessing size in the nanometer range or some property dependent on the nanoscale size of a device component.

nanomanufacturing—manufacturing of nanotechnology products.

nanomaterials—materials whose size is in the nanometer range or whose components are in the nanometer range.

nanomedicine—medical breakthroughs dependent on nanotechnology.

nanometer (nm)—one billionth of a meter. A strand of DNA is approximately 2 nm in diameter.

nanoparticle—a piece of matter with at least one dimension between about 1 and 100 nm.

nanoscale—the size range from about 1 to 100 nm.

nanoshell—nanomaterial with a core of silica and a metallic outer layer and can be decorated with molecular probes for cancer-related compounds. Nanoshells can be used to image tumors and for theranostics. Nanoshells are also used to provide targeted delivery of drugs to tumor cells.

nanostructure—a collection of atoms, molecules, or nanoparticles whose relative positions are engineered chemically or physically on the nanometer or micron scale.

nanotechnology—"the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale" (NNI, 2010).

nanotoxicity—toxicity of a material resulting from its nanoscale properties as distinguished from the toxicity caused by the same material in bulk form.

nanotube—most commonly, this term refers to tubes formed by graphitic sheets of carbon atoms. Carbon nanotubes can be as narrow as just a few nanometers and up to hundreds of microns in length or longer. Carbon nanotubes can be conducting or semiconducting depending on their atomic arrangement, and individual nanotubes are very strong.

nanowire—a wire whose diameter is in the nanoscale range. Nanowires can range from several hundred nanometers in length to many microns and longer. Nanowires can be synthesized or fabricated from many different materials.

neoplastic—possessing characteristics of abnormal new tissue growth.

PEGylated—property of being coated with molecules of polyethylene glycol or functionalized polyethylene glycol.

pharmacodynamics—the effects of a drug and its metabolites on a living organism, including how the effects are modified by characteristics of the organism treated with the drug.

pharmacokinetics (PK)—the chemical evolution of a drug after administration to a living organism, including lifetimes, metabolic products, biodistribution, and routes of clearance from the organism.

phase I clinical trial—a clinical trial in a small number of patients in which the toxicity and dosing of an intervention are assessed.

phase II clinical trial—a clinical trial in which the safety and preliminary efficacy of an intervention are assessed.

phase III clinical trial—a large clinical trial in which the safety and efficacy of an intervention are assessed in a large number of patients. The Food and Drug Administration generally requires new drugs to be tested in phase III trials before they can be put on the market.

photolithography—method by which precise patterns are transferred from a master pattern (a mask) onto a substrate. This method is used to fabricate computer chips, for example.

quantum dots—nanocrystals made from one or more types of semiconducting materials. Quantum dots specifically refer to nanocrystals that fluoresce when excited with light. These nanocrystals are used as imaging labels for biological imaging and have several advantages over tra-

ditional organic fluorescent dyes, including longer fluorescence lifetimes and the ability to fluoresce when excited with a broad range of excitation wavelengths.

reticuloendothelial system (RES)—a component of the immune system consisting primarily of macrophages and monocytes.

self-assembly—process that occurs when a system—often of similar shape, size, or composition—move from a disordered to a more ordered state as the system approaches equilibrium. Characteristics that work to effect the ordered state include physical and chemical properties such as polarizability, surface charge, and hydrophobicity and forces such as capillary action.

target moiety—a part of a molecule that is selected for binding of an antibody or drug for an assay, treatment, or medical device (such as an imaging contrast enhancer).

theranostics—molecular complexes that enable both a diagnostic test and delivery of a therapeutic agent simultaneously in a living organism.

therapeutic target—the destination for delivery, binding, or therapeutic effect of a drug or other medical treatment.

transgenic—possessing, referring to, or being a gene from one species residing in another species.

tumor necrosis factor (TNF)—a protein involved in inflammation, it causes cell death, including by causing cell death of tumor cells.

xenograft—cells, tissues, or organs that have been transferred from one species to another.

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A

Agenda

National Cancer Policy Forum Workshop
Institute of Medicine
July 12–13, 2010

The Liaison Capitol Hill Hotel
"The Hill" Conference Room
415 New Jersey Avenue NW
Washington, DC 20001

DAY 1, July 12

8:30 am	Breakfast Available
9:00 am	Welcome **Edward Benz**, planning committee chair, *Dana Farber Cancer Institute*
Session 1	***Introduction to Nanotechnology and Nanomedicine*** *Moderator*: **Edward Benz**, *Dana Farber Cancer Institute*
9:15 am	**Historical View of Nanotechnology and Nanomedicine** **Mauro Ferrari**, *University of Texas Health Science Center–Houston*
9:45 am	**The NCI Nanotechnology Alliance for Cancer: Making Personalized Cancer Medicine a Reality** **Anna Barker**, *National Cancer Institute*
10:15 am	BREAK
10:30 am	**Cancer Nanotechnology Beyond the NCI** **Steven Curley**, *MD Anderson Cancer Center*

Session 2 ***Clinical Research and Translational Science—Accommodating and Enabling Nanotechnology***
Moderator: **Steven Curley**, *MD Anderson Cancer Center*

Each speaker is asked to comment on the flow of translational research:
- What does a clinical investigator planning trials incorporating nanotechnology need to know?
- What will it take to get there?

Clinical Research Perspective
Speakers are asked to address the following questions:
- What do clinical researchers need to know about nanotechnology?
- What tests must nano-materials themselves undergo?
- What are potential and known risks with use of nanotechnology and how are unknowns being addressed?
- Are there real advantages to nanotechnology (as diagnostics, screening tools, therapeutics, etc.)?

11:00 am **Nanoparticles as Therapeutic Platforms**
Steve Libutti, *Albert Einstein School of Medicine*

11:30 am **Biologic Barriers to In Vivo Nanomedicine Delivery: Major Hurdles for Clinical Translation**
King Li, *The Methodist Hospital Research Institute*

12:00 pm LUNCH

Industry Perspective
Speakers are asked to address the following questions:
- How are companies thinking about moving nanotechnology products through the pipeline from proof of concept to development for clinical trials?
- What is the current state of preclinical studies in testing efficacy and toxicity?
- What are the long-term effects of these incredibly stable products?
- Is it known what happens in degradation processes?

1:00 pm **The *nab*-Platform: From Bench to the Clinic and Beyond**
Neil Desai, *Abraxis Biosciences*

Preventive Medicine Perspective
Speakers are asked to address the following questions:
- What issues, opportunities, and known efforts exist within this domain?

– What challenges and unique enhancements does nanotechnology provide in this area?
– How can nanotechnology be used to improve health (i.e., through environmental remediation or to make safer foods, etc.)?

1:30 pm **Nanotechnology and Cancer Prevention**
Ernie Hawk, *MD Anderson Cancer Institute*

Diagnostics and Therapeutics Discovery and Development Perspective
Speakers are asked to address the following questions:
– What issues, opportunities, and known efforts exist within this domain?
– What challenges and unique enhancements does nanotechnology provide in this area?

2:00 pm **Opportunities for Reproducibility and Uniformity of Therapeutics and Vaccines Using Templated Nanomanufacturing Methods**
Joseph DeSimone, *University of North Carolina*

2:30 pm **James Heath,** *California Institute of Technology*

3:00 pm BREAK

Radiology and Laboratory Medicine Perspective
Speakers are asked to address the following questions:
– What issues, opportunities, and known efforts exist within this domain?
– What challenges and unique enhancements does nanotechnology provide in this area?

3:15 pm **Microfluidic Approaches for Single Cell Analysis**
Scott Manalis, *Massachusetts Institute of Technology*

3:45 pm **Magnetic Nanoparticles and Magnetic Resonance: From Contrast Agents to Assays to Sensors**
Lee Josephson, *Harvard University*

4:15 pm **Panel Discussion**—Ideas for making progress in the next 2, 10, and 20 years
All session speakers

4:45 pm Adjourn until Tuesday

DAY 2, July 13

8:00 am Breakfast Available

8:20 am Welcome Back

Session 3 ***Government Research Initiatives, Regulation, and International Standards***
Moderator: **Mauro Ferrari**, *University of Texas Health Science Center–Houston*

Government Research Initiatives
Speaker is asked to address the following questions:
- Describe the role of the Nanotechnology Characterization Laboratory and how it may evolve over the next 10 years.
- Describe some challenges overcome and current challenges facing the laboratory.
- How do these lessons extend to other government research initiatives?

8:30 am **NCI's Nanotechnology Characterization Lab: Lessons Learned and Future Directions**
Scott McNeil, *Nanotechnology Characterization Laboratory*

9:00 am **Discussion** with Scott McNeil, Piotr Grodzinski, Mauro Ferrari, and Anna Barker

9:30 am BREAK

International Standards: Cooperative Research and Regulation: Lessons and Challenges
Speakers are asked to address the following questions:
- What lessons can US regulators learn from regulation of nanotechnology in other countries?
- What policies support cooperative research internationally?
- What policies support product development and regulation internationally?

9:45 am **Crossroad of Nanomedicine: Nanosafety and Policy**
Yuliang Zhao, *Chinese Academy of Sciences, and Research Center for Cancer Nanotechnology*

10:15 am **Successful Transfer of Innovative Technologies from Lab-Patient-Routine Use: Lessons Learnt and Global Opportunities**
Ruth Duncan, *Cardiff, UK*

10:45 am **Nanomedicines Challenges and Opportunities in a Global Development Environment**
Rogério Gaspar, *Research Institute for Medicines and Pharmaceutical Sciences*

11:15 am Discussion

11:30 am WORKING LUNCH (boxed lunches available)

Regulatory Challenges and Safety
Speakers are asked to address the following questions:
– What are regulators looking for?
– How is nanotechnology being handled?
– What concerns do the public have and how are they best addressed?

11:45 am **Kristen Kulinowski**, *Rice University*

12:15 pm **Jonathan Sackner-Bernstein**, *Food and Drug Administration*

12:45 pm Discussion

1:00 pm **Workshop Wrap-up**
Moderator: **Mauro Ferrari**, *University of Texas Health Science Center–Houston*

1:15 pm Adjourn

B

Speaker and Planning Committee Biographies

Anna D. Barker, Ph.D., served as the Deputy Director of the National Cancer Institute (NCI) and as the NCI's Deputy Director for Strategic Scientific Initiatives until September 2010. She was a member of the Executive Committee of the NCI and participated in all aspects of strategic planning, decision making, and program implementation to achieve the NCI's mission. Dr. Barker has led the planning, development, and implementation of a number of strategic scientific and technology initiatives and partnerships that emphasize innovation, trans-disciplinary teams, and convergence of scientific disciplines to enable progress against cancer. These programs also stress the development and application of advanced technologies, the synergy of large scale and individual initiated research, novel partnerships, and translation of discoveries into new interventions to detect, prevent, and treat cancer more effectively.

At the NCI Dr. Barker collaborated on the planning and implementation for the Institute's major initiative in bioinformatics (the Cancer Bioinformatics Grid); planned and initiated an NCI-wide program to establish biospecimen standards and best practices; and planned and launched the Clinic Proteomics Technology Initiative for Cancer that is focused on the development, standardization, and deployment of the technologies, reagents, and protocols needed to enable the systematic and reproducible identification of cancer biomarkers. She also co-developed The Cancer Genome Atlas (TCGA) Pilot Program jointly with the National Human Genome Research Institute (NHGRI). TCGA's long term goal is to define all significant genetic changes in most if not all cancers. The pilot phase

of this program has demonstrated "proof of concept" for large scale disease focused genomics and will move to an expanded phase in late 2009. In addition, under her leadership the NCI planned and deployed the Nanotechnology Alliance for Cancer, a major network in cancer nanotechnology dedicated to the development and application of nanotechnologies to areas ranging from new generation diagnostics to drug delivery and imaging. More recently, Dr. Barker led a planning effort to enable the convergence of the physical sciences (physics, mathematics, physical chemistry, and engineering) with cancer biology. As a result the NCI will establish a network of Physical Oncology Centers to provide physical scientists and cancer biologists the opportunity to collaboratively study cancer at all scales. All of these programs broadly engage the extramural cancer research communities.

She co-led with the FDA the establishment of the NCI–FDA Interagency Oncology Task Force (IOTF). The focus of the IOTF is the identification of scientific and process gaps in the regulatory pathways for cancer interventions—and joint science-based approaches to addressing these barriers. Dr. Barker also leads the NCI's efforts in strategic international research programs in Latin America and China.

Dr. Barker has a long history in research and the leadership and management of advanced research and development in the academic, non-profit, and private sectors. She served as a senior executive at Battelle Memorial Institute for 18 years where she developed and led large groups of scientists and technical staff working in drug discovery and development, pharmacology, clinical trials, and biotechnology, including several NCI sponsored research programs. As a Senior Vice President at Battelle, she pioneered several programs in cancer research in collaboration with the NCI, including the use of advanced research models for evaluating new drug candidates and novel models for pharmacologic and toxicological evaluation. In the private sector, she was a co-founder and CEO of a public biotechnology company focused in experimental therapeutics development of novel agents to control reactive oxygen damage; and a private cancer technology company.

She has served as a member of the National Coalition of Cancer Research; a Partner and member of the Board of Directors of C-Change; chairperson of the C-Change Cancer Research Team; founding member of the Department of Defense (DOD) Breast Cancer Research Program (BCRP) Integration Panel and chairperson of the BCRP Integration Panel; in a number of capacities for the American Association for Cancer Research (AACR), including the Board of Directors and chairperson of the Public Science Policy and Legislative Affairs Committee for over 10 years; a member of the NCI's Board of Scientific Counselors, Division of Cancer Etiology, and chairperson of the Cancer Center Support Review Study

Section; member of private boards of directors; and in varying capacities for a number of additional organizations. Dr. Barker has received a number of awards for her contributions to cancer research, cancer patients, professional and advocacy organizations, and the ongoing national effort to prevent and cure cancer.

Dr. Barker completed her M.A. and Ph.D. at the Ohio State University, where she trained in immunology and microbiology. Her research interests include experimental therapeutics, tumor immunology, and free-radical biochemistry in cancer etiology and treatment.

Edward J. Benz, Jr., M.D., is a pioneering academic hematologist whose early work, showed that messenger RNA defects caused a common congenital anemia, thalassemia. This was the first demonstration that molecular biology could be applied to the study of human diseases. He has subsequently achieved international renown for his research in the area of human red cell disorders, gene regulation, and membrane biology. He remains an active NIH funded investigator and clinician.

As an educator, Benz has been an active teacher and mentor throughout his career. He has trained over 50 mentees in his laboratory, many of whom now hold senior faculty or leadership positions in academia, industry, or private practice. In recognition of his contributions as a mentor, he was named winner of the 2007 American Society of Hematology Mentoring Award in Basic Science.

Benz also has had an impact as a national leader, having served as president of the prestigious American Society of Clinical Investigation and president of the American Society of Hematology. Currently, he is the President of the Association of American Cancer Institutes. He has co-edited the top-rated textbook in the field of hematology, and educated an entire generation about the application of molecular biology to clinical medicine through his lectures, review articles, and book chapters. In November of 2000, Dr. Benz was appointed President of Dana-Farber Cancer Institute. He holds the Richard and Susan Smith Professorship in Medicine and is a Professor of Pediatrics and a Professor of Pathology at Harvard Medical School.

Steven A. Curley, M.D., is Professor of Surgery, the Charles B. Barker Chair in Surgery, Program Director of the Gastrointestinal Multidisciplinary Care Center, Chief of Gastrointestinal Tumor Surgery, and Director of the Surgical Oncology Fellowship Program at the University of Texas MD Anderson Cancer Center. Dr. Curley received his undergraduate education at the University of New Mexico, where he graduated Magna Cum Laude, Phi Beta Kappa with a Bachelor of Science degree in Biology and Biochemistry. He received his medical degree at the University of Texas

Medical School at Houston, being elected to Alpha Omega Alpha as a junior, and then completed a general surgery residency at the University of New Mexico in Albuquerque. Following residency, he completed a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Center, where upon completion of his fellowship, he joined the faculty. Dr. Curley is a Fellow of the American College of Surgeons and serves in the following groups: Colorectal Cancer Collaborative Clinical Trials, Colorectal Cancer Commission on Cancer Fellowship, Commission on Cancer Liver Disease Site Team, and the American College of Surgeons Hepatobiliary Oncology Group. Dr. Curley's major areas of interest are surgical treatments for patients with primary and metastatic liver cancers; the role of hepatitis B and C virus in hepatocellular cancer tumorigenesis; the development of novel treatment approaches for patients with primary and metastatic liver malignancies; neoadjuvant and adjuvant treatment approaches in patients with primary and metastatic hepatobiliary malignancies; and the development of targeted nanoparticle therapies in patients with advanced malignant diseases. Dr. Curley pioneered the clinical studies leading to FDA approval of radiofrequency ablation to treat unresectable primary and metastatic hepatobiliary malignancies. This has led to multidisciplinary trials to combine resection and radiofrequency ablation with adjuvant and neoadjuvant systemic and regional treatment to further improve patient outcome. He has been involved in the development of radiofrequency ablation equipment and treatment algorithms for patients with unresectable primary and metastatic hepatic malignancies. He has developed novel surgical techniques that have significantly reduced blood loss and operative time associated with major liver resections. He is principal investigator (PI) on a phase I/II trial studying ADI-PEG 20, a novel targeted drug therapy to treat patients with unresectable cancer. He has initiated a new basic science research program to study biodistribution of carbon nanotubules and gold nanoparticles in normal and tumor tissue, and to use carbon nanotubules and gold nanoparticles as targeted therapy to treat malignant tumors with a novel external radiofrequency field generator. He is also PI of a program to screen high-risk hepatitis B and C virus patients for hepatocellular cancer in the Campania region of Italy. This study has been awarded a European Community Grant to extend the study to other high-risk areas in Europe. Dr. Curley has successfully translated from basic and preclinical studies human clinical trials for hepatic isolation infusion treatments for unresectable hepatocellular cancer and direct intratumoral injection of a collagen matrix mixed with chemotherapeutic agents. Dr. Curley has served a term as Chairman of the Graduate Medical Education Committee at the University of Texas MD Anderson Cancer Center and is currently the Course Director of the Research Ethics seminars and a member of the Clinical

Council Subcommittee on Clinical Research Funding. Dr. Curley serves as an Associate Section Editor for the *Annals of Surgical Oncology.* He is also a member of the Editorial Boards for the following journals: *Annals of Surgical Oncology, The Cancer Bulletin, International Journal of Surgical Sciences, Cancer Reports, Bulletin of the National Cancer Institute of Italy, European Journal of Surgical Science, International Journal of Surgical Investigation.*

Neil P. Desai, Ph.D., is currently senior vice president of Global Research and Development at Abraxis Bioscience, in Los Angeles, California, where he is responsible for the development of the company's growing product pipeline and the development of the company's intellectual property portfolio. Dr. Desai is an inventor of ABI's nanotechnology and nanoparticle–albumin bound (nab™) drug delivery platform, was primarily responsible for the development of its nantechnology drug, Abraxane, and the discovery of the novel targeted biological pathway utilized by nab™-drugs. This platform has been clinically proven to enhance the efficacy and safety of cytotoxic drugs through a novel targeted biological pathway and is the first protein-based nanotechnology product to be approved by the FDA for the treatment of cancer.

Prior to joining ABI in 1999, Dr. Desai was senior director of biopolymer research at VivoRx, Inc., and VivoRx Pharmaceuticals, Inc. (predecessor companies of ABI), where he worked on the early discovery and development of Abraxane, developed novel encapsulation systems for living cells, and was part of the team that performed the world's first successful encapsulated islet cell transplant in a diabetic patient.

Dr. Desai has more than 20 years of experience in the research and development of novel drug delivery systems and biocompatible polymers. He holds over 100 issued patents and peer-reviewed publications and has made over 150 presentations at scientific meetings. Dr. Desai holds an M.S. and Ph.D. in chemical engineering from the University of Texas at Austin, and a B.S. in chemical engineering from the University Institute of Technology in Mumbai, India.

Joseph M. DeSimone, Ph.D., is the Chancellor's Eminent Professor of Chemistry at the University of North Carolina at Chapel Hill and William R. Kenan Jr. Professor of Chemical Engineering at North Carolina State University. DeSimone is also an Adjunct Member at Memorial Sloan-Kettering Cancer Center in New York. DeSimone has published over 270 scientific articles and has over 115 issued patents in his name with over 120 patents pending.

In 2005, DeSimone was elected into the National Academy of Engineering and the American Academy of Arts and Sciences. DeSimone has received 40 major awards and recognitions including the 2009 NIH Direc-

tor's Pioneer Award; the 2009 North Carolina Award, the highest honor the State of North Carolina can bestow to recognize notable achievements of North Carolinians in the fields of Literature, Science, the Fine Arts, and Public Service; the $500,000 Lemelson–MIT Prize for Invention and Innovation; the *2008 Tar Heel of the Year* by the Raleigh News & Observer; the *2007 Collaboration Success Award* from the Council for Chemical Research; the 2005 ACS Award for Creative Invention; the *2002 John Scott Award* presented by the City Trusts, Philadelphia, given to "the most deserving" men and women whose inventions have contributed in some outstanding way to the "comfort, welfare and happiness" of mankind; the *2002 Engineering Excellence Award by DuPont*; the *2002 Wallace H. Carothers Award* from the Delaware Section of the ACS; 2000 Oliver Max Gardner Award from the University of North Carolina, given to that person, who in the opinion of the Board of Governors' Committee, ". . . during the current scholastic year, has made the greatest contribution to the welfare of the human race."

Among DeSimone's notable inventions is an environmentally friendly manufacturing process that relies on supercritical carbon dioxide instead of water and bio-persistent surfactants (detergents) for the creation of fluoropolymers or high-performance plastics, such as Teflon®. In 2002, DeSimone, along with Dr. Richard Stack, a cardiologist at Duke, cofounded *Bioabsorbable Vascular Solutions* (BVS) to commercialize a fully bioabsorbable, drug-eluting stent. BVS was acquired by *Guidant Corporation* in 2003 and these stents are now being evaluated in a series of international clinical trials led by Abbott, enrolling over 1,000 patients as of November 2009, for the treatment of coronary artery disease.

With the PRINT technology developed in the DeSimone lab, DeSimone's group is now heavily focused on bringing the precision, uniformity, and mass production techniques associated with the fabrication of nanoscale features found in the microelectronics industry to the nanomedicine field for the fabrication and delivery of vaccines and therapeutics for the treatment and prevention of diseases.

DeSimone recently launched Liquidia Technologies (www.liquidia.com) which now employs almost 50 people in Research Triangle Park and has raised over $50 ,million in venture financing. DeSimone's laboratory and the PRINT technology recently became a foundation for the new $20 million Carolina Center for Cancer Nanotechnology Excellence funded by the National Cancer Institute. DeSimone received his B.S. in Chemistry in 1986 from Ursinus College in Collegeville, PA and his Ph.D. in Chemistry in 1990 from Virginia Tech.

Ruth Duncan, Ph.D., Professor of Cell Biology and Drug Delivery, was until September 2008 (when she retired from the University) at the Welsh

School of Pharmacy, Cardiff University, UK where she was Director of the Centre for Polymer Therapeutics. She currently sits on a number of institutional and international advisory boards and committees, and she holds the honorary positions of Professor Emerita in Cardiff University and Visiting Professor at the University of Greenwich.

After Ph.D. studies at Keele University on the mechanism of endocytosis (1979), she established an interdisciplinary group (CRC Polymer Controlled Drug Delivery Group) interested in the rational design of polymeric anticancer conjugates. Later after joining Farmitalia Carlo Erba (became Pharmacia) in Milan as Head of New Technologies, she was involved the Project Team Leader responsible for transfer of the first polymer anticancer conjugates and imaging agents arising from this work into clinical trial. She has contributed more than 250 scientific articles and patents, and has been a recipient of many awards including the Pfizer Research Award for Pharmaceutical Sciences, Young Investigator Award of the Controlled Release Society, the Interdisciplinary Award of the Royal Society for Chemistry UK, the Berlin-Brandenburg Academy of Sciences Monika Knutzner Award for Innovative Cancer Research, a Princess Takamatsu Cancer Foundation Lecturer, and the GSK International Achievement Award. In 2009, she received The APSTJ Nagai International Woman Scientist Award and was made a Fellow of the Association of Pharmaceutical Science and Technology (APSTJ) Japan. She is also an elected corresponding member of the Academy of Sciences and Literature, Mainz.

In 1996, she established the ongoing series of biennial International Conferences on Polymer Therapeutics: From Laboratory to Clinic (latest 2010 Valencia, Spain). She was elected Co-Chair of the Gordon Research Conference on Drug Carriers in Biology and Medicine in 1998, and in 2004 was elected the Science Chair of the British Pharmaceutical Conference.

Ruth Duncan chaired the Steering Committee of the European Science Foundation's Forward Look on Nanomedicine (2005). She has also acted as Co-Chair of the European Science Foundation Research Conferences (2006 and 2008) and Summer Schools in Nanomedicine (2007 and 2009) and continues to promote interdisciplinary Nanomedicine Research Conferences and Training Schools.

She is a past member of the CPS subcommittee of the UK Medicines and Health Regulatory Agency and is currently a member of the European Medicines Agency AD Hoc Advisory Committee on Nanomedicine and the EC DG SANCO SCENHIR working group for definition of "Nanomaterials."

Mauro Ferrari, Ph.D., serves as President and CEO of The Methodist Hospital Research Institute, where he holds the Ernest Cockrell Jr. Distin-

guished Endowed Chair. He is also Professor of Internal Medicine at the Weill Cornell Medical College, Adjunct Professor of Experimental Therapeutics at the University of Texas MD Anderson Cancer Center, Professor of Bioengineering at Rice University, Adjunct Professor of Biomedical Engineering at UT Austin, and President of The Alliance for NanoHealth in Houston.

Dr. Mauro Ferrari is a founder of biomedical nano/micro-technology, especially in their applications to drug delivery, cell transplantation, implantable bioreactors, and other innovative therapeutic modalities. In these fields, he has published more than 200 peer-reviewed journal articles and 6 books. He is the inventor of more than 30 issued patents, with about thirty more pending in the United States and internationally. His contributions have been recognized by a variety of accolades, including: the Presidential Young Investigator Award of the National Science Foundation; the Shannon Director's Award of the National Institutes of Health; the Wallace H. Coulter Award for Biomedical Innovation and Entrepreneurship; and the Italiani nel Mondo Award from the Italian Ministry of Foreign Affairs. His career research and development portfolio totals over $50 million, including support from the NCI, NIH, DoD, NASA, NSF, DARPA, DoE, the State of Texas, and the State of Ohio, The Ohio State University, and several private enterprises. He began his academic career at the University of California, Berkeley, where he tenured in Material Science, Civil Engineering, and Bioengineering. Upon recruitment to the Ohio State University, he served as the Edgar Hendrickson Professor of Biomedical Engineering, Professor of Internal Medicine, Mechanical Engineering, Materials Science and Associate Vice President, Health Sciences Technology and Commercialization, Associate Director of the Dorothy M. Davis Heart and Lung Research Institute and Director of the Biomedical Engineering Center. Upon recruitment to Houston, he served as Professor and Chair of the Department of Nanomedicine at the University of Texas Health Science Center.

Dr. Ferrari also served as Special Expert on Nanotechnology at the National Cancer Institute in 2003–2005, providing leadership into the formulation, refinement, and approval of the NCI's Alliance for Nanotechnology in Cancer, currently the world's largest program in medical nanotechnology.

Dr. Ferrari's degrees are in Mathematics (Padova, 1985, Italy), and Mechanical Engineering (U.C. Berkeley, M.S. 1987, and Ph.D. 1989). He attended medical school at the Ohio State University (2002–2003).

Dr. Ferrari is an academic–entrepreneur, with several companies that originated from his laboratory. He currently serves on the Board of Director three companies: Nanomedical Systems of Austin TX; Leonardo Biosystems of Houston Texas, and Arrowhead Research Corporation.

Rogério Sá Gaspar, Ph.D., is currently Full Professor in Pharmaceutics at the Faculty of Pharmacy at the University of Lisbon and Member of the Coordination Board of iMed.UL, in which he also coordinates the Nanomedicine & Drug Delivery System research unit. He is currently also a consultant to the pharmaceutical industry. Early in his career, both at the University of Coimbra and whilst undertaking his Ph.D. studies at the Université Catholique de Louvain in Brussels, he developed an interest in advanced drug delivery systems. He has continued to work in this area, and he has more than 20 years experience in the design and evaluation of nanoparticles and liposomes for drug (e.g., Leishmaniasis and cancer) and nucleic acid (cytosolic) delivery. At the University of Coimbra he integrated the CNC (Centre for Neurosciences and Cell Biology, Department of Biotechnology and Molecular Biology) where he started in 1994 the Drug Carriers Unit.

Throughout his career, Rogério Gaspar was also called upon to support the development of Portuguese medicines regulatory strategy with his participation on numerous national and European committees, including his role as Vice-chairman of the Medicines National Committee and Vice-chairman of the Management Board at INFARMED (1996–1999 and 2000–2002 respectively) or as an advisory expert of the European Medicines Agency (EMEA) and member of CPMP (now CHMP) in the period 1995–1999. In 2000 Gaspar was chairman of the Working Group on Human Medicines of the European Council (European Union) that concluded the political agreement on the European Clinical Trials Directive (2000). In 2000–2002 he was also member of the Management Board of EMEA.

These aspects that give a unique perspective of both nanomedicines research and development and the regulatory process and are responsible for frequent invitations for conferences and working groups in Europe, Asia, and USA (including FDA workshop in nanotechnology, March 2008).

In addition, Rogério Gaspar was Chairman of the Spanish–Portuguese Local Chapter of the Controlled Release Society (2002–2005), and member of the expert panel that developed the European Science Foundation's Forward Look on Nanomedicine (2003–2005). Co-chairman of the 2006 ESF Conference on Nanomedicine, he also chaired the next European Research Conference on Nanomedicine (European Science Foundation, 2008) and chaired the ESF Summer School for advanced Training in Nanomedicine held in Lisbon 2009.

After more than 21 years at the University of Coimbra he is since 2006 at the University of Lisbon, where he is starting a number of projects along his main research interests (cancer and inflammation).

Piotr Grodzinski, Ph.D., is Director of NCI Alliance for Nanotechnology in Cancer at the National Cancer Institute in Bethesda, Maryland. He

coordinates program and research activities of the Alliance which dedicated $144 million over 5 years to form interdisciplinary centers as well as fund individual research and training programs targeting nanotechnology solutions for improved prevention, detection, and therapy of cancer.

Dr. Grodzinski is a materials scientist by training, but like many others found biotechnology and nanotechnology fascinating. In the mid-nineties, he left the world of semiconductor research and built a large microfluidics program at Motorola Corporate R&D in Arizona. The group made important contributions to the development of integrated microfluidics for genetic sample preparation with its work being featured in Highlights of Chemical Engineering News and Nature reviews. After his tenure at Motorola, Dr. Grodzinski was with Bioscience Division of Los Alamos National Laboratory where he served as a Group Leader and an interim Chief Scientist for DOE Center for Integrated Nanotechnologies (CINT). In his current capacity at the National Institutes of Health (NIH), he is also co-chairing Trans-NIH Nanotechnology Task Force, which is coordinating the nanotechnology efforts across 27 institutes of the agency with the budget over $200 million per year.

Dr. Grodzinski received his Ph.D. in Materials Science from the University of Southern California, Los Angeles in 1992. He is an inventor on 15 patents and published 47 peer-reviewed papers, 7 book chapters, and delivered over 100 invited conference presentations. Dr. Grodzinski has been an invited speaker and served on the committees of numerous bio- and nano-MEMS conferences in the past years.

Ernest T. Hawk, M.D., M.P.H., head of MD Anderson's Division of Cancer Prevention and Population Sciences, leads a division of nearly 500 employees including approximately 80 faculty members within four departments, three centers, and the recently established Duncan Family Institute for Cancer Prevention and Risk Assessment. The Institute's resources are helping scientists to accelerate the pace of discovery and the translation of findings to the clinic and community, advancing MD Anderson's mission in cancer prevention research, practice, and education.

Dr. Hawk was named Boone Pickens Distinguished Chair for Early Prevention of Cancer at MD Anderson in December 2009. Prior to joining the institution in December 2007, he held several positions at the National Cancer Institute (NCI) in Bethesda, Maryland. He began work at NCI in 1996 and most recently served as director of the Office of Centers, Training, and Resources. His other NCI posts included chief and medical officer in the Gastrointestinal and Other Cancers Research Group, medical officer in the Chemoprevention Branch, and chair of the Translational Research Working Group.

He has been involved in a wide range of preclinical and clinical

chemoprevention research, including studies of nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, and agent combinations. He has earned numerous awards for his work, including the prestigious NCI Research Award for Distinguished Achievement in Cancer Prevention.

A native of Detroit, Michigan, Dr. Hawk earned his bachelor's and medical degrees at Wayne State University and his master of public health degree at Johns Hopkins University. He completed an internal medicine internship and residency at Emory University, a medical oncology clinical fellowship at the University of California, San Francisco, and a cancer prevention fellowship at NCI.

Dr. Hawk has served as a peer reviewer for 30 different scientific and medical journals; has authored more than 120 articles in leading books and journals including the *New England Journal of Medicine*, *JNCI*, *Gastroenterology*, *Journal of Clinical Oncology*, and *Circulation;* and currently serves as deputy editor for *Cancer Prevention Research* and member of the scientific advisory committee for *Prevention Magazine.*

James R. Heath, Ph.D., is the Elizabeth W. Gilloon Professor and Professor of Chemistry at Caltech, and Professor of Molecular & Medical Pharmacology at UCLA, and Director of the National Cancer Institute's NanoSystems Biology Cancer Center.

Heath received a B.Sc. degree in 1984 (Baylor University) and his Ph.D. in Chemistry (Rice University) in 1988 where he was the principal student involved in the Nobel Prize–winning discovery of C_{60} and the fullerenes. Heath was a Miller Fellow at the University of California, Berkeley, from 1988–1991, and on the Technical Staff at IBM Watson Labs from 1991–1993. In 1994 he joined the faculty at UCLA. He founded the California NanoSystems Institute in 2000 and served as its Director until moving to Caltech. Heath has investigated quantum phase transitions, and he has developed architectures, devices, and circuits for molecular electronics. His group has recently been applying their advances on nanoelectronics circuitry toward addressing problems in cancer.

He has received a number of awards, including a Public Service Commendation from Governor Gray Davis, the Sackler Prize, the Spiers Medal, the Feynman Prize, the Jules Springer Prize, and the Arthur K. Doolittle Award. He has founded or co-founded several companies, including NanoSys, MTI, MoB, and Homestead Clinical Corporation, and he serves on the board of a number of organizations, including the Board of Scientific Advisors of the National Cancer Institute.

Lee Josephson, Ph.D., focuses his research on the chemistry and design of multimodal imaging agents (agents detectable by two modalities), including fluorescent, radioactive, and magnetic nanoparticle probes.

They have designed a class of reagents termed MSAP's, or Multimodal, Single Attachment Point reagents, that permit the attachment of multiple reporter groups (fluorochromes, chelates, polymers) at a single point of a targeting substrate. The targeting substrate can be a peptide, protein, or drug. MSAP reagents permit the synthesis of complex, multimodal imaging agents in a single step and through the modification at a single site of a targeting substrate.

A second, related research interest is development of multimodal probes for imaging cell death. These include the magneto/fluorescent nanoparticle, Anx-CLIO(Cy5.5), a magneto/fluorescent nanoparticle for imaging the phosphatidylserine expressed on apoptotic cells. Another multimodal probe developed for imaging cell death is GadoTO. GadoTO consists of a vital fluorochrome (TO-PRO 1) to which a reporter gadolinium chelate has been attached. GadoTO is the first of a new class of agents termed multimodal vital fluorochromes (MVFs). MVFs consist of two parts: (i) a vital fluorochrome that permeates the porous membranes of necrotic cells and is then retained with cells by binding DNA, and, (ii) a paramagnetic or radioactive reporter that makes the MVF detectable by PET, MRI, or SPECT. An understanding of biology of the cell death response, as it pertains to the binding of the probes they have synthesized, is an important interest of my laboratory.

A third research interest is the synthesis and activity self-activating viridin (SAV) prodrugs. These inactive polymeric prodrugs slowly release viridins like wortmannin. SAV prodrugs are highly effective in three classes of animal models; those for asthma, arthritis, and cancer xenografts. SAV prodrugs have been synthesized with multiple fluorescent reporters so that the disposition of the fate of the various components of the prodrug can be monitored in vivo.

Kristen Kulinowski, Ph.D., is a Faculty Fellow in the Department of Chemistry at Rice University and Director for External Affairs for the Center for Biological and Environmental Nanotechnology (CBEN). She currently serves as the Director of the International Council on Nanotechnology (ICON), an international, multi-stakeholder organization whose mission is to develop and communicate information regarding potential environmental and health risks of nanotechnology thereby fostering risk reduction while maximizing societal benefit. She has experience as a chemical researcher, educator, curriculum developer, administrator, outreach coordinator, and policy fellow.

Since 2004, Dr. Kulinowski has been actively engaged in developing and promoting the International Council on Nanotechnology (ICON) which provides a neutral forum in which experts from academia, governments, industry, and nonprofit organizations can explore questions of

nanotechnology's impact on environment, health, and safety (EHS). She directed an effort that resulted in the web publication of the first publicly available database of citations to peer-reviewed papers on nano EHS. Other activities of ICON include a survey of best practices for nanomaterial handling in the workplace and a public portal of information on nanotechnology EHS.

Dr. Kulinowski has extensive experience in science education, particularly in developing innovative curricula at the undergraduate level, and developed Rice's first introductory undergraduate course on nanotechnology. From 2002–2004 Dr. Kulinowski served as CBEN Executive Director for Education, developing and managing an educational outreach portfolio of programs for audiences that range from middle school children to adults. During this time the center established itself as a national leader in nanotechnology educational outreach.

Prior to joining CBEN, she was a lecturer in chemistry at California Polytechnic State University, San Luis Obispo, for three years and came to Rice as an instructor in chemistry in 1998. In 2001, she was selected by the Optical Society of America and SPIE—The International Society for Optical Engineering—as their Congressional Science Fellow and worked in the DC office of a member of the US House of Representatives on issues including weapons of mass destruction, anti-terrorism legislation, and domestic nuclear power security. She was instrumental in shepherding through new legislation on the stockpiling of potassium iodide near nuclear power plants. As a longtime volunteer with American Red Cross Disaster Relief Services, Dr. Kulinowski brought food and water to rescue workers at the Pentagon on September 11, 2001.

Dr. Kulinowski is highly sought after as a speaker and has given invited talks on issues of nanotechnology environmental health and safety and science policy throughout the US, Europe, and the Middle East. She has consulted with governments and governmental advisory bodies regarding responsible nanotechnology, and she serves as chair of the ASTM International Subcommittee E56.03 on Environment, Health, and Safety. Dr. Kulinowski earned a B.S. in chemistry at Canisius College and her M.S. and Ph.D. in chemistry at the University of Rochester.

King C. Li, M.D., F.R.C.P., M.B.A., graduated from Faculty of Medicine, University of Toronto in 1981 and finished his residency in 1986 also at the University of Toronto. Dr. Li is currently a Professor of Radiology at Weill Medical College of Cornell University and MD Anderson Foundation Distinguished Chair of Radiology at the Methodist Hospital in Houston, Texas. Before joining the Methodist he was the Associate Director of the NIH Clinical Center and the Chief of Radiology and the Imaging Sciences Program. Dr. Li was on faculty in Stanford University for 10 years prior

to joining the NIH. Dr. Li's main research interest is in molecular imaging, molecular image guided therapy, and integrating imaging with tissue analysis for studying systems biology. He has 9 issued and 6 pending patents, has won over 10 different awards from 4 different professional organizations and has given numerous invited lectures. He has published over 100 scientific articles, 5 book chapters, and 1 monograph and has received grants from government, industry, and private sources.

Steven K. Libutti, M.D., FACS, received his A.B. from Harvard College and his M.D. from the College of Physicians and Surgeons of Columbia University where he was inducted into the Alpha Omega Alpha medical honor society. He completed his internship, surgical residency, and was Chief Resident at the Presbyterian Hospital in New York. Following residency, he completed a fellowship in Surgical Oncology and Endocrine Surgery at the National Cancer Institute (NCI) prior to becoming a Clinical Investigator and then Senior Investigator and Chief of the Tumor Angiogenesis Section in the Surgery Branch, NCI. He is currently the Director of the Montefiore-Einstein Center for Cancer Care, Associate Director of the Albert Einstein Cancer Center, and Professor and Vice-Chairman of Surgery and Professor of Genetics at the Montefiore Medical Center and the Albert Einstein College of Medicine in New York.

Dr. Libutti has received numerous honors and awards throughout his medical career including the Blakemore Award for Outstanding Research in Surgery, the NCI's Technology Transfer Award, The NCI Director's Gold Star Award, the NCI Director's Intramural Innovation Award, and the NIH Director's Award. Dr. Libutti has been voted a "Top Doctor in America" and to New York Magazine's list of the Top Doctors in New York.

He has served on the editorial boards for the journals *Expert Opinion in Biological Therapy, Molecular Imaging, Translational Medicine, The Cancer Journal, Surgery* (Society Editor*), Endocrine Related Cancer, Molecular Cancer,* and *The Journal of Immunotherapy*. His research interests include tumor angiogenesis, anti-angiogenic gene therapy, gene expression profiling, regional therapy of malignant tumors, isolation and characterization of unique tumor cytokines, and studies of the tumor microenvironment.

Dr. Libutti is a member of numerous professional societies relating to cancer research and served as Chair of the steering committee for the Trans-NIH Angiogenesis Research Program (TARP). Dr. Libutti's clinical expertise is in the management of malignancies of the liver, pancreas, and GI tract, and in applying laparoscopic surgery to managing patients with cancer. In addition, Dr. Libutti is an internationally recognized expert in endocrine surgery and provides surgical consultation and treatment for

patients with disorders of the thyroid, parathyroid, adrenal glands, and for endocrine tumors arising in the pancreas.

Dr. Libutti has published over 200 peer reviewed journal articles, 16 book chapters, and has been invited to give numerous presentations and lectures. He also holds five US patents.

Scott Manalis, Ph.D., received the B.S. degree in physics from the University of California, Santa Barbara and the Ph.D. degree in applied physics from Stanford University. He is currently a member of the Koch Institute for Integrative Cancer Research and a professor in the departments of biological and mechanical engineering at MIT. His laboratory uses microscale and nanoscale technologies to develop quantitative and real-time techniques for biomolecular detection and single cell analysis. Dr. Manalis was the recipient of the Presidential Early Career Award for Scientists and Engineers (PECASE) from the Department of Defense. He has also been selected by Technology Review magazine as one of the 100 innovators under the age of 35 whose work and ideas "will have a deep impact on how we live, work and think in the century to come."

Scott E. McNeil, Ph.D., serves as Director of the Nanotechnology Characterization Laboratory for NCI at Frederick where he coordinates preclinical characterization of nanomaterials intended for cancer therapeutics and diagnostics. Prior to joining NCI–Frederick (i.e. SAIC–Frederick), he served for three years as Senior Scientist in the Nanotech Initiatives Division at SAIC where he transitioned basic nanotechnology research to government and commercial markets. He advises industry and state and US governments on the development of nanotechnology and is a member of several governmental and industrial working groups related to nanotechnology policy, standardization, and commercialization. Dr. McNeil's professional career includes tenure as an Army Officer, with tours as Chief of Biochemistry at Tripler Army Medical Center, as a Combat Arms officer in the Gulf War. He is an invited speaker to numerous nanotechnology-related conferences and has six patents pending related to nanotechnology and biotechnology. He received his bachelor's degree in chemistry from Portland State University and his doctorate in cell biology from Oregon Health Sciences University.

John Mendelsohn, M.D., combines experience in clinical and laboratory research with administrative expertise in preparing the University of Texas MD Anderson Cancer Center for the next century. Since becoming president in 1996, he has recruited a visionary management team and implemented new priorities for integrated programs in patient care, research, education, and cancer prevention. For almost three decades,

Dr. Mendelsohn has been at the forefront in understanding how growth factors regulate the proliferation of cancer cells by activating receptors on the surface of the cells. He developed cetuximab, a specific monoclonal antibody that blocks epidermal growth factor (EGF) and transforming growth factor-alpha binding to EGF receptors, thereby inhibiting activation of receptor tyrosine kinase and preventing the growth factors from stimulating cell growth and division. His research led to the first clinical trial with an antireceptor therapy and an anti-tyrosine kinase therapy. Dr. Mendelsohn was born in Cincinnati, Ohio, and earned a bachelor's degree in biochemical sciences magna cum laude from Harvard College in 1958. After spending a year in Scotland as a Fulbright Scholar, Dr. Mendelsohn received a medical degree cum laude from Harvard Medical School in 1963. Between 1963 and 1970, he took residency training in internal medicine and completed a research fellowship in oncology at Washington University Medical School in St. Louis, Missouri. From 1970 to 1985, he was on the University of California, San Diego (UCSD) faculty, rising from assistant professor to professor of medicine at UCSD in less than 9 years. He was instrumental in establishing and funding a National Cancer Institute–designated Cancer Center at UCSD, which he directed from its inception in 1976 until he went to Memorial Sloan-Kettering Cancer Center in 1985. At Memorial Sloan-Kettering, Dr. Mendelsohn chaired, reorganized, and expanded its Department of Medicine. He also extended the landmark research that he began at UCSD to clarify at the molecular level how cetuximab alters growth-signaling pathways and cell functions. He also demonstrated the additive antitumor effects of EGF receptor inhibition plus chemotherapy or radiotherapy. As a result of successful clinical trials, the Food and Drug Administration approved cetuximab (Erbitux) for the treatment of colon cancer in 2004 and head and neck cancer in 2006. Dr. Mendelsohn served as the founding editor-in-chief of *Clinical Cancer Research*, a monthly translational research journal published by the American Association for Cancer Research, and he has been a member of the editorial boards of other leading scientific journals. He has authored more than 200 scientific papers and articles for journals and textbooks and is senior editor of *The Molecular Basis of Cancer*. His awards include the Joseph H. Burchenal and the Dorothy P. Landon awards from the American Association for Cancer Research and the David A. Karnofsky Prize from the American Society of Clinical Oncology. He is a member of the Institute of Medicine of the US National Academies.

John Niederhuber, M.D., is a nationally renowned surgeon and researcher who has dedicated his four-decade career to the treatment and study of cancer—as a professor, cancer center director, National Cancer Advisory

Board chair, external advisor to the NCI, grant reviewer, and laboratory investigator supported by NCI and the National Institutes of Health.

Most recently, Dr. Niederhuber served as Director of the NCI (2005–2010). He has also served as NCI's Chief Operating Officer and Deputy Director for Translational and Clinical Sciences. In addition, Dr. Niederhuber served as Chair of the National Cancer Advisory Board (NCAB) from 2002–2004.

In addition to his management and advisory roles, Dr. Niederhuber has remained involved in research, through his laboratory on the National Institutes of Health (NIH) campus. Under his leadership, the Tumor and Stem Cell Biology Section, which is a part of the Cell and Cancer Biology Branch of NCI's Center for Cancer Research, is studying tissue stem cells as the cell-of-origin for cancer.

Dr. Niederhuber also holds a clinical appointment on the NIH Clinical Center Medical Staff.

As a surgeon, Dr. Niederhuber's clinical emphasis is on gastrointestinal cancer, hepatobiliary (liver, bile duct, and gall bladder) cancer, and breast cancer. He is recognized for his pioneering work in hepatic artery infusion chemotherapy and was the first to demonstrate the feasibility of totally implantable vascular access devices.

Jonathan Sackner-Bernstein, M.D., is associate director for post market operations in the Center for Devices and Radiologic Health at the US Food and Drug Administration (FDA). At FDA, his charges include oversight of post market operations and serving as champion of the reorganization of the Center for Devices & Radiologic Health (CDRH) into a matrix structure. With that later responsibility comes direct involvement in premarket, compliance and regulatory aspects of medical device development as well.

Over the prior 18 years, his experiences have included leadership in cutting edge medical research. Dr. Sackner-Bernstein serves as a consultant to the US FDA, serving for 2 years as an ad hoc member of the Cardiovascular and Renal Drugs Advisory committee and now as a standing member of the Medical Devices Dispute Resolution Committee of CDRH. He serves as a safety consultant for large pharma and biotech.

As an investigator, Dr. Sackner-Bernstein seeks out innovative approaches, with a particular interest in extending therapies from one therapeutic area to another.

Not afraid to speak out when supported by data, as reflected by his recent book *Before It Happens to You*, he has had sufficient experience to value the power of working within systems and with colleagues to effect solutions to key problems.

Ralph Weissleder, M.D., Ph.D., is a Professor at Harvard Medical School and Director of the Center for Systems Biology, the newest Massachusetts General Hospital (MGH) thematic research center. He is also the Director of the MGH Center for Molecular Imaging Research, and is clinically active as an Attending Interventional Radiologist in the MGH Department of Radiology. He is an active member of many Boston-area research communities, including the Department of Systems Biology at Harvard Medical School, the Broad Institute of Harvard and the Massachusetts Institute of Technology, the Dana-Farber-Harvard Cancer Center, and the Harvard Stem Cell Institute (HSCI).

He has published over 500 publications in peer-reviewed journals, has authored and co-authored several textbooks, and holds 15 patents. He is a founding member of the Society for Molecular Imaging Research and served as its President in 2002. His work has been honored with numerous awards including the J. Taylor International Prize in Medicine, the Millennium Pharmaceuticals Innovator Award, the AUR Memorial Award, the ARRS President's Award, the Society for Molecular Imaging Lifetime Achievement Award, and the Academy of Molecular Imaging 2006 Distinguished Basic Scientist Award.

Yuliang Zhao, Ph.D., is Professor and Director, CAS Key Lab for Biomedical Effects of Nanomaterials & Nanosafety, Institute of High Energy Physics, Chinese Academy of Sciences (CAS), and National Center for Nanosciences and Technology of China. Dr. Zhao's degrees are in chemistry and physics. He moved to Chinese Academy of Sciences from RIKEN (Japan) as a Hundred Elite Professor in 2001. He is a founder of CAS Nanosafety Lab, and also one of the earliest scientists who proposed and studied nanotoxicology. He is mainly focused on the biomedical effects of nanostructure/nanoscale materials, including (1) the biomedical functions of manufactured nanomaterials, (2) the toxicological effects of nanomaterials including identification of nano-hazards, drafting regulatory frameworks and nano-standards for safety issues on nanotechnology, and establishing standard procedures for safety assessment of nano-products for government agencies, (3) surface chemistry of nanoparticles and their novel properties for the purposes of enhancing the biomedical functions or reducing potential toxicity, and (4) molecular dynamics theoretical simulation and modeling the dynamic processes of the interplay between nano-systems and bio-systems.